AD NUMBER

ADB070947

NEW LIMITATION CHANGE

TO

Approved for public release, distribution unlimited

FROM

Distribution authorized to U.S. Gov't. agencies only; Official Operational use; Jan 1983. Other requests shall be referred to AFAMRL/TMB, WPAFB, OH 45433.

AUTHORITY

AFAMRL notice, 11 may 1983

AFAMRL-TR-82-87

(12)

AD B070947

DEVELOPMENT OF CANDIDATE CHEMICAL SIMULANT LIST: THE EVALUATION OF CANDIDATE CHEMICAL SIMULANTS WHICH MAY BE USED IN CHEMICALLY HAZARDOUS OPERATIONS

ARTHUR D. LITTLE, INC.
ACORN PARK
CAMBRIDGE, MA 02140

DECEMBER 1982

AIR FORCE AEROSPACE MEDICAL RESEARCH LABORATORY
AEROSPACE MEDICAL DIVISION
AIR FORCE SYSTEMS COMMAND
WRIGHT-PATTERSON AIR FORCE BASE, OH 45433

NOTICES

When US Government drawings, specifications, or other data are used for any purpose other than a definitely related Government procurement operation, the Government thereby incurs no responsibility nor any obligation whatsoever, and the fact that the Government may have formulated, furnished, or in any way supplied the said drawings, specifications, or other data, is not to be regarded by implication or otherwise, as in any manner licensing the holder or any other person or corporation, or conveying any rights or permission to manufacture, use, or sell any patented invention that may in any way be related thereto.

Federal Government agencies and their contractors registered with Defense Technical Information Center should direct requests for copies of this report to:

Defense Technical Information Center
Cameron Station
Alexandria, Virginia 22314

TECHNICAL REVIEW AND APPROVAL

AFAMRL-TR-82-87

This technical report has been reviewed and is approved for publication.

FOR THE COMMANDER

Roger C. Inman

ROGER C. INMAN, Colonel, USAF
Chief
Toxic Hazards Division
Air Force Aerospace Medical Research Laboratory

SECURITY CLASSIFICATION OF THIS PAGE (When Data Entered)

REPORT DOCUMENTATION PAGE

READ INSTRUCTIONS BEFORE COMPLETING FORM

1. REPORT NUMBER: AFAMRL-TR-82-87	2. GOVT ACCESSION NO.: AD-B078 947L
3. RECIPIENT'S CATALOG NUMBER:	
4. TITLE (and Subtitle): Development of Candidate Chemical Simulant List: The Evaluation of Candidate Chemical Simulants Which May Be Used in Chemically Hazardous Operations	5. TYPE OF REPORT & PERIOD COVERED: Final Report, Work Order #1 Jun 15, 1982 - Dec 15, 1982
	6. PERFORMING ORG. REPORT NUMBER: 87638-01
7. AUTHOR(s): Arthur D. Little, Inc. Acorn Park Cambridge, MA 02140	8. CONTRACT OR GRANT NUMBER(s): F33615-81-D-0508/0001
9. PERFORMING ORGANIZATION NAME AND ADDRESS: Arthur D. Little, Inc. Acorn Park Cambridge, MA 02140	10. PROGRAM ELEMENT, PROJECT, TASK AREA & WORK UNIT NUMBERS: 63745F 27220027 & 62202F 63020155
11. CONTROLLING OFFICE NAME AND ADDRESS: Air Force Aerospace Medical Research Laboratory, Aerospace Medical Division, Air Force Systems Command, Wright-Patterson AFB, Ohio 45433	12. REPORT DATE: December 1982
	13. NUMBER OF PAGES: 144
14. MONITORING AGENCY NAME & ADDRESS (if different from Controlling Office)	15. SECURITY CLASS. (of this report): UNCL
	15a. DECLASSIFICATION/DOWNGRADING SCHEDULE

16. DISTRIBUTION STATEMENT (of this Report)

Distribution limited to U. S. Government agencies only, Official Operational Use, January 1983. Other requests for this document must be referred to AFAMRL/THB.

17. DISTRIBUTION STATEMENT (of the sbstract entered in Block 20, if different from Report)

18. SUPPLEMENTARY NOTES

Contact: Ms Marilyn E. George
AFAMRL/THB (255-5150) (area code 513)
WPAFB, OH 45433

19. KEY WORDS (Continue on reverse side if necessary and identify by block number)

Chemical defense
Chemical simulants list
Toxicology
Uptake chemical simulants

20. ABSTRACT (Continue on reverse side if necessary and identify by block number)

Nonhazardous chemical simulants of chemical warfare agents are needed by the United States Air Force (USAF) to test the effectiveness of protective equipment and decontamination procedures both in the laboratory and under full operational conditions. Selected candidate simulants, when dispersed, should mimic the physical characteristics of the actual agents as closely as possible, but induce no physiological effects in exposed personnel. Additionally, their uptake should be quantifiable in biological fluids, preferably urine or saliva.

DD FORM 1 JAN 73 1473 EDITION OF 1 NOV 65 IS OBSOLETE

SECURITY CLASSIFICATION OF THIS PAGE (When Data Entered)

In an initial task (Report No. AFAMRL-TR-82-28), seven candidates were proposed, four in the volatile category, the remaining three in the intermediate volatility range. All candidates in the low and non-volatile range were eliminated. This report is a continuation and supplementation of the initial task. The objectives of this task were threefold:

(1) to provide additional data for the proposed candidate simulants dipentene, methyl benzoate and benzyl alcohol by means of in-depth literature searches encompassing both computerized data bases and a manual search of the older literature;

(2) to fully evaluate twelve possible candidate simulants under more flexible simulant criteria; and,

(3) to develop a list of candidate simulants in the low and non-volatile categories.

Computerized literature searches were conducted for the twelve possible candidate simulants under more flexible intake simulant criteria as well as for dimethyl methylphosphonate, a compound selected for evaluation by the USAF. The twelve possible candidates included: cyclohexanone, n-dodecanethiol, methyl salicylate, dihexyl ether, dypnone, n-aminopropyl morpholine, n-(2-hydroxyethyl) morpholine, butyl salicylate, di(2-ethyl hexyl) ether, 2-undecanol, 2-hydroxyethyl-n-octyl sulfide and n,n-diethyl-m-toluamide.

Full assessments of the potential health hazards associated with exposure to n-dodecanethiol, methyl salicylate, butyl salicylate and n,n-diethyl-m-toluamide were completed. All of these compounds meet the majority of USAF criteria for candidate simulants. Cyclohexanone was disqualified for reasons of toxicity, while the available toxicolcgical data for the seven remaining candidates were considered inadequate for full assessment of hazard.

A list of candidate chemical simulants in the low and non-volatile categories (vapor pressure 0.03 - 10^{-4} mm Hg) was developed. Six chemicals: diethyl sebacate, dibenzyl ether, isoamyl benzoate, anisyl phenylacetate, n-octyldecanethiol and phenylethyl phenylacetate are proposed as possible candidate simulants. All of these proposed candidate simulants meet a majority of the physical chemical specifications, have low orders of toxicity and most have documented human exposure data and/or are approved for use in foods and other consumer products.

SUMMARY

Nonhazardous chemical simulants of chemical warfare agents are needed by the United States Air Force (USAF) to test the effectiveness of protective equipment and decontamination procedures both in the laboratory and under full operational conditions. Selected candidate simulants, when dispersed, should mimic the physical characteristics of the actual agents as closely as possible, but induce no physiological effects in exposed personnel. Additionally, their uptake should be quantifiable in biological fluids, preferably urine or saliva.

In an initial task (Report No. AFAMRL-TR-82-28), seven candidates were proposed, four in the volatile category, the remaining three in the intermediate volatility range. All candidates in the low and non-volatile range were eliminated. This report is a continuation and supplementation of the initial task. The objectives of this task were threefold:

(1) to provide additional data for the proposed candidate simulants dipentene, methyl benzoate and benzyl alcohol by means of in-depth literature searches encompassing both computerized data bases and a manual search of the older literature;

(2) to fully evaluate twelve possible candidate simulants under more flexible simulant criteria; and,

(3) to develop a list of candidate simulants in the low and non-volatile categories.

Computerized literature searches were conducted for the twelve possible candidate simulants under more flexible intake simulant criteria as well as for dimethyl methylphosphonate, a compound selected for evaluation by the USAF. The twelve possible candidates included: cyclohexanone, n-dodecanethiol, methyl salicylate, dihexyl ether, dypnone, n-aminopropyl morpholine, n-(2-hydroxyethyl) morpholine, butyl salicylate, di(2-ethyl hexyl) ether, 2-undecanol, 2-hydroxyethyl-n-octyl sulfide and n,n-diethyl-m-toluamide.

Full assessments of the potential health hazards associated with exposure to n-dodecanethiol, methyl salicylate, butyl salicylate and n,n-diethyl-m-toluamide were completed. All of these compounds meet the majority of USAF criteria for candidate simulants. Cyclohexanone was disqualified for reasons of toxicity, while the available toxicological data for the seven remaining candidates were considered inadequate for full assessment of hazard.

A list of candidate chemical simulants in the low and non-volatile categories (vapor pressure 0.03 - 10^{-4} mm Hg) was developed. Six chemicals: diethyl sebacate, dibenzyl ether, isoamyl benzoate, anisyl phenylacetate, n-octyldecanethiol and phenylethyl phenylacetate are proposed as possible candidate simulants. All of these proposed candidate simulants meet a majority of the physical chemical specifications, have low orders of toxicity and most have documented human exposure data and/or are approved for use in foods and other consumer products.

PREFACE

This is the final report of work performed by Arthur D. Little, Inc., for the Air Force under Work Order #1, Contract F33615-81-D-0508, Work Unit 63020155, "Mutagenic, Teratogenic, and Carcinogenic Potential of Air Force Chemicals." This report describes accomplishments from June 15, 1982, to December 15, 1982. Andrew Sivak, Ph.D. was Program Manager for the program. Muriel Goyer, M.S. was Task Manager for this Work Order. Key personnel involved with this project included: Alan Branfman, Ph.D., Marjory Chadwick, Ph.D. Elizabeth Cole, B.A., Daniel Ehntholt, Ph.D., Margaret Miller, M.L.S., Kenneth Sidman, M.S., Warren Lyman, Ph.D., Kathleen Thrun, M.S., Janice Thyer, M.A. Marilyn E. George, Biochemical Toxicology Branch, Toxic Hazards Division, Aerospace Medical Research Laboratory, was technical monitor for the Air Force.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF ABBREVIATIONS, ACRONYMS AND SYMBOLS

AAS	Atomic absorption spectroscopy
Acetyl CoA	A coenzyme that takes part in many biological acetylation reactions
ACGIH	American Conference of American Governmental Industrial Hygienists
ADP	Adenosine diphosphate
AFID	Alkali flame ionization detector
ASTM	American Society for Testing and Materials
atm	Atmosphere (760 Torr)
ATP	Adenosine triphosphate
BaP	Benzo[a]pyrene
BUN	Blood urea nitrogen
bw	Body weight
C	Celsius
CAS Reg. No.	Numeric designation assigned by the American Chemical Society's Chemical Abstracts Service which uniquely identifies a specific chemical compound
cc	Cubic centimeter
CFR	Code of Federal Regulations
CI	Chemical ionization mode (mass spectrometry)
CL	Ceiling limit value
cm	Centimeter (10^{-2} meter)
CNS	Central nervous system
CO	Carbon monoxide
CO_2	Carbon dioxide
Cp	Centipoise
CW	Chemical warfare
d	dextrorotary; solution rotates plane of polarized light to the right
da	day(s)
derm	dermal
dl	racemic; optically inactive
ECD	Electron capture detector
EI	Electron impact ionization mode (mass spectrometry)
F	Fahrenheit
F_1, F_2	Offspring of first, second, etc., filial generation
FDA	Food and Drug Administration (U.S.A.)
FEMA	Flavoring Extract Manufacturer's Associatic
FID	Flame ionization detector
FPD	Flame photometric detector
ft	Foot
g	Gram(s)
g pg	Guinea pig
GC	Gas chromatography
GC/AFID	Gas chromatography/alkali flame ionization detector
GC/ECD	Gas chromatography/electron capture detector
GC/MS	Gas chromatography/mass spectrometry
GC/NPD	Gas chromatography/nitrogen-phosphorus detector (Alkali flame ionization detector)
GC/PID	Gas chromatography/photoionization detector
GC/TC	Gas chromatography/thermionic detector

GRAS	Generally recognized as safe
HCl	Hydrochloric acid
Hg	Mercury
hr	Hour(s)
HPLC	High-pressure liquid chromatography
HPLC/UV	High-pressure liquid chromatography/Ultraviolet spectroscopy
ID	Internal diameter
in	Inch
ip	Intraperitoneal
IR	Infrared spectroscopy
IRI	Serum immunoreactive insulin
IRR	Irritant
iv	Intravenous
kg	Kilogram (10^3 grams)
l	Levorotary; solution rotates plane of polarized light to the left
L	Liter
LC	Liquid chromatography
LC_{50}	The concentration required to kill 50% of test individuals
LC/EC	Liquid chromatography/electrochemical detector
LDH	Serum lactic dehydrogenase
LDLo	Lowest reported lethal dose
LOD	Loss on drying
LOI	Loss on ignition
LRMS	Low resolution mass spectrometry
m	Meter
MCA	Manufacturing Chemists Association
MCT	Medium chain fatty acid
mg	Milligram (10^{-3} gram)
min	Minute
ml	Milliliter (10^{-3} liter)
mm	Millimeter (10^{-3} meter)
mM	Millimoles
MS	Mass spectrometry
MW	Molecular weight
N	Normal; a solution containing one gram equivalent weight per liter
NaCl	Sodium chloride
NDIR	Non-dispersive infrared analyzer
ng	Nanogram (10^{-9} gram)
nm	Nanometer (10^{-9} meter)
OD	Outer diameter
pH	A measure of hydrogen ion concentration
po	Oral route

ppb	Part(s) per billion

one part in 10^9. For gaseous mixtures, a volume:volume basis is typically used and 1 ppb is on the order of 1 $\mu g/m^3$:

$$\mu g/m^3 = ppb \times \frac{RT}{MW}$$

where RT = 22.4 L/mole at 0° and 1 atm
= 24.5 L/mole at 25° and 1 atm

For liquid materials, a weight:volume basis is most commonly used and 1 ppb = 1 µg/L (~ 1 µg/kg for liquids with density ~ 1). For solid materials, a weight:weight basis is most commonly used and 1 ppb = 1 µg/kg.

ppm	Part(s) per million

one part in 10^6 (see ppb)
1 ppm ~ 1 mg/m^3 gaseous
1 ppm = 1 mg/L liquid
1 ppm = 1 mg/g solid

rbt	Rabbit
rpm	Revolutions per minute
RTECS	Registry of Toxic Effects of Chemical Substances
sc	Subcutaneous
sec	Second
SGOT	Serum glutamic oxalacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
TCD	Thermal conductivity detector
TDLo	Lowest reported toxic dose
TLC	Thin layer chromatography
TOC	Total organic carbon content
TWA	Time-weighted average
µg	Microgram (10^{-6} gram)
µCi	Microcurie (10^{-6} curie)
µL	Microliter (10^{-6} liter)
µM	Micrometer (10^{-6} meter)
UV	Ultraviolet spectroscopy
vol.%	Parts in 100 parts by volume
wk	Week(s)
w/v	Weight in volume
w/w	Weight in weight
°	Degrees, as 37°
%	Percent
>	Greater than
<	Less than
~	Approximately
♂	Male
♀	Female
λ	Wavelength

INTRODUCTION

This report summarizes the continuation and supplementation of a previous task (Report No. AFAMRL-TR-82-28) conducted for the United States Air Force (USAF) in which Arthur D. Little, Inc. assisted the USAF in developing a list of candidate chemical simulants to test protective equipment and procedures involved in chemical warfare (CW) training exercises. The agents simulated were the nerve agents sarin, soman and tabun. The essential and desirable intake simulant characteristics requested to be matched by the USAF are given in Table 1.

This supplemental task involved an in-depth literature search encompassing both computerized data bases and a manual search of the older literature for the compounds dipentene, methyl benzoate and benzyl alcohol. The manual searches included Chemical Abstracts 1907 to 1966, Biological Abstracts 1926 to 1966, Index Medicus 1897 to 1966 and Nutrition Abstracts and Reviews 1931 to 1965. Each of these indices was searched under the following entries: dipentene; limonene; p-menta-1,8-diene; methyl benzoate; benzoates, methyl ester; benzyl alcohol; alcohols; and benzyl compounds. The material uncovered in these searches was evaluated and is presented in the section of this report entitled "Supplemental Data on Three Previously Proposed Candidate Simulants."

Computerized literature searches were also conducted for twelve possible candidate simulants under more flexible intake simulant criteria as well as for dimethyl methylphosphonate, a compound selected for evaluation by the USAF. The twelve possible candidates included: cyclohexanone, n-dodecanethiol, methyl salicylate, dihexyl ether, dypnone, n-aminopropyl morpholine, n-(2-hydroxyethyl)morpholine, butyl salicylate, di(2-ethyl hexyl)ether, 2-undecanol, 2-hydroxyethyl-n-octylsulfide and n,n-diethyl-m-toluamide.

Evaluations of potential health hazards for n-dodecanethiol, methyl salicylate, butyl salicylate and n,n-diethyl-m-toluamide follow in later sections of this report. Cyclohexanone was disqualified for reasons of toxicity (Gupta et al., 1979; Koeferl et al., 1981; Rengstorff et al., 1972) as well as several positive mutagenic findings, including 2- to 4-fold increases in chromosome aberrations in human lymphocytes cultured with 5 µg/L cyclohexanone (Dyshlovoi et al., 1981; Massoud et al., 1980; Collins, 1971). Available toxicological data for the seven remaining candidates were considered inadequate for full assessment of hazard. Available toxicological information for these compounds was limited to acute studies conducted with laboratory animals, and for the most part, fewer than twenty total citations were contained in the computerized data bases examined. Available data for these compounds are presented in Appendix A.

Thirdly, a list of candidate chemical simulants in the low and non-volatile categories (vapor pressure 0.03 - 10^{-4} mm Hg) was developed. Appropriate sources were searched for chemicals with boiling points greater than 250°C which we estimated would be consistent with vapor pressures of 10^{-4} to 0.03 mm Hg. These chemicals were subsequently screened for acute toxicity criteria. Six of these chemicals, diethyl sebacate, dibenzyl ether, isoamyl benzoate, anisyl phenylacetate, n-octyldecanethiol and phenylethyl phenylacetate are proposed as possible candidate simulants.

TABLE 1

ESSENTIAL AND DESIRABLE INTAKE SIMULANT CHARACTERISTICS

ESSENTIAL CHARACTERISTICS:

- A candidate intake simulant must be a material which is in use by intentional application to humans, or for which human effects data are known.
- Physical/chemical properties must be within the following ranges at 20°C:

	Volatile	Intermediate	Low	Non-volatile
Volatility (mg/m^3):	2700-15,000	300-2700	1-300	0-1
Vapor Pressure (mm Hg):	0.27-2.1	0.03-0.27	10^{-4}-0.03	0-10^{-4}
Boiling Point (°C):	150-200	200-250	300^{+}	300^{+}
Melting Point (°C):	<15	<15	<15	<15
Viscosity (cp)	<20	<20	<20	<20

- The compound should not have an LD_{50} (24 hr) less than 1000 mg/kg by oral and dermal routes of application.
- Liquid must pass the unbroken skin.
- The ratio of the minimum dose causing recognizable pathological change to the maximum dose to which a human can be exposed should not be less than 100.
- The compound should be negative to most tests of mutagenicity and should not be positive in a chronic dose carcinogenicity trial (2 yr).
- The compound should be cleared from tissues in 24 to 48 hr after application, with a constant fraction of the applied dose excreted. Not less than 90% of the administered dose should be accounted for in balance studies.
- Analytical method must be sensitive to 5 ug/ml or less of the compound in urine.

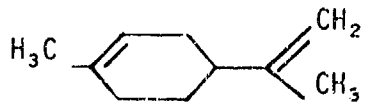
DESIRABLE CHARACTERISTICS:

- The compound should have a flash point allowing it to be disseminated by an explosive device.
- The compound should have a melting point of less than 0°C.
- The compound must not decompose rapidly on exposure to light, heat, oxygen or water.
- The compound should not damage paints, plastics, textiles or rubbers.
- The compound should not have an LD_{50} (24 hr) less than 2000 mg/kg by oral and dermal routes of application.
- The ratio of the minimum dose causing recognizable pathological change to the maximum dose to which a human can be exposed should not be less than 1000.
- Analytical method should be capable of being automated.
- Analytical method should be as simple as possible
- The compound should be visibly detectable by the addition of a catalyzing dye or under ultraviolet light.
- Characteristics of removal from skin, clothing and equipment (decontaminatable) identical to its analog war agent.
- The compound should have a cost of commercial manufacture of less than 500 $/kg delivered.

A listing of candidate simulants disqualified due to anticipated difficulties in detection can be found in Appendix B. Full evaluations of potential health effects were not done for these candidates. Candidates unacceptable primarily for reasons of toxicity, or lack of any information thereof, are listed in Appendix C.

SUPPLEMENTAL DATA ON THREE PREVIOUSLY PROPOSED CANDIDATE SIMULANTS

The information presented in the following pages includes supplemental data on dipentene, methyl benzoate and benzyl alcohol not included in our earlier report to the USAF (Report No. AFAMRL-TR-82-28). This additional information was uncovered through in-depth computerized and manual literature searches conducted on these compounds.

Simulant:	Dipentene; Cyclohexene, 1-methyl-4-(1-methylethenyl)-
Formula:	
CAS Reg. No.:	138-86-3
Molecular Weight:	136.23
Chemical State (20°C):	colorless liquid
Liquid Density (g/cc):	d^{20} 0.845
Vapor Density (compared to air):	4.66
Freezing/Melting Point (°C):	-97°
Boiling Point (°C):	174.6°
Flash Point (°C):	45°
Vapor Pressure (mm Hg at 20°C)	1.4 (Lyman et al., 1982, Chap. 14, method 2)
Volatility (mg/m^3):	1.0×10^4
Viscosity (cp at 20°C):	0.74 (Lyman et al., 1982, Chap. 22, method 3)
Odor:	pleasant, lemon-like odor
Action on Metals or Other Materials:	A solvent for resins, waxes, rubber; will penetrate and attack thermoplastics (e.g., polystyrene); no action on nitrile rubber; non-corrosive to metals
Reference Source(s):	Furia and Bellanca (1975); MCA (1972); Sax (1979); Lyman et al. (1982).

DIPENTENE (Supplement)

Potential Health Effects

Human Data

- Skin Irritation/Sensitization

Closed patch tests with 4% l-limonene in petrolatum produced no skin irritation in human volunteers after 48 hours (Opdyke, 1978a). A maximization test conducted with 4% l-limonene produced no sensitization reaction in 23 test subjects (Opdyke, 1978a).

Henry (1933, 1938) described a form of dermatitis which occurred in workers preparing celery for canning. Among 391 employees, 119 (30.4%) developed dermatitis. All the cases occurred in individuals involved in wet processes for cleansing the celery. Limonene, a constituent of celery oil, was suggested as the causative factor, but no confirmation tests were conducted.

Several investigators have implicated dipentene as one of several possible constituents of turpentine responsible for human sensitivity reactions to turpentine (Rokstad, 1947; Hellerström et al., 1953, 1957; Pirila et al., 1964; Pirila and Siltanen, 1958).

Hellerström and coworkers (1957) indicated d-limonene to be one of four skin-active compounds in Swedish turpentine; the three other constituents were Δ^3-carene, α-pinene and β-pinene, with Δ^3-carene being considered by these investigators to be the most eczematogenic constituent by far.

Earlier work by Hellerström and Lundin (1951) had shown by means of patch tests in individuals sensitive to turpentine that the test responses were in direct relation to the degree of oxidation that the turpentine had undergone. Patch tests in these turpentine-sensitive individuals with freshly distilled turpentine and its fractions were negative.

Pirila et al. (1964) tested both freshly distilled and oxidized dipentene samples in patch tests in 30 individuals not sensitive to turpentine; oxidized samples contained 8 to 26% hydroperoxides. The lowest concentration of freshly distilled, unoxidized dipentene eliciting a reaction (weak) was 50% or greater; concentrations of 70-80% produced redness, often combined with edema at 24 hours. With oxidized material, the primary irritant effect increased with increasing hydroperoxide content. The lowest hydroperoxide concentration eliciting reactions varied from 1 to 8%, the threshold being about 2% for most subjects.

The work by the Hellerström and Pirila groups indicate that the eczematogenic effects of turpentine is dependent on its content of oxidation products. The role of dipentene in this reaction has not been fully elucidated. Pirila and Siltanen (1958) concluded that oxidized Δ^3-carene is the major contributor to the sensitization reactions and that the weaker responses seen with three remaining terpenes implicated as causative agents are probably due to low level contamination with Δ^3-carene.

Opdyke (1976) reported that the addition of d-limonene to a sensitizing aldehyde (e.g., citral, cinnamic aldehyde) appeared to "quench" the induction of sensitization in humans. The aldehydes, when tested alone, induced positive sensitization reactions.

Animal Studies

- Acute Toxicity

Acute oral and dermal LD_{50} values for l-limonene in the rat and rabbit, respectively, were both greater than 5 g/kg (Opdyke, 1978a).

- Skin Irritation

Application of undiluted l-limonene to intact or abraded rabbit skin for 24 hours under occlusion was moderately irritating (Opdyke, 1978a).

- Subchronic Inhalation

Gardner (1925) reported that exposure by inhalation of two healthy albino rabbits to dipentene fumes for 56 treatments over a 71-day period produced some slight irritation of mucous membranes, anemia and "slightly hazy" lens. Necropsy of one rabbit indicated mild glomerular congestion and cloudy swelling of the convoluted tubules of the kidney and mild congestion of the large bronchi and the base of the lungs. The first 10 exposures over a two week period consisted of pouring 30 ml dipentene into a shallow dish which was placed beneath a wire-mesh cage suspended inside a wooden box. The exposure regimen was then changed to suspension of a sponge soaked with the dipentene inside the animal's cage. The rabbits were treated in this manner for 22 exposures over the next 25 days. The amount of dipentene was then increased to 50 ml for 14 treatments but was then dropped to 20 ml for the final 10 treatments because of findings of "mild leucocytosis" and "a tendency to leucopenia" with the 50 ml exposures.

Pinching and Doving (1974) noted a conspicuous pattern of morphological changes (darkening and shrinkage of cell bodies) in the mitral cells of the olfactory bulb in Wistar rats continuously exposed by inhalation to an ambient concentration of 6.6×10^{-8} M limonene for 5 weeks beginning at two weeks of age. No manifestations of toxicity were reported.

- Induction of Reticuloendothelial System

Stimulation of the reticuloendothelial system by d-limonene was observed in guinea pigs given intramuscular injections of d-limonene (10 mg every 5th day for 5 weeks). Phagocytic activity of macrophages was measured against tubercle bacilli (BCG). A 3+ response (of possible 4+) was scored (Gözsy and Kátó, 1957).

- Carcinogenicity/Tumor Promotion

Stoner et al. (1973) examined the ability of d-limonene to induce primary lung tumors in 6-8 week-old strain A mice. Two groups of mice were given intraperitoneal injections of d-limonene in tricaprylin 3 times weekly

for 8 weeks. Total doses for the two treatment groups were 24 and 4.8 g/kg/mouse. Mice were killed 24 weeks after the first injection. A negative pulmonary tumor response was observed.

Roe and Peirce (1960) reported tumor promoting activity in strain 101 mice for an 80% terpene fraction of expressed orange oil consisting mainly of d-limonene. Twenty mice received a single 300 µg application of DMBA (9,10-dimethyl-1,2-benzoanthracene in acetone). After a 3 week interval, weekly applications of 0.25 ml of the terpene fraction were begun. Papillomas developed after 11 weeks, and by the 33rd week of secondary treatment, there were 29 papillomas on 8 of 15 survivors compared to 1 papilloma on 1 of 16 survivors in the control group. A squamous-cell carcinoma was seen in the terpene group during the 36th week of treatment.

Nacino et al. (1975) also reported promoting activity for 80% citrus oil (consisting mainly of d-limonene) in Japanese SDDy-strain mice initiated with a single application of DMBA (300 µg in acetone) as well as in 3/5 Sprague Dawley rats in which promotion was started 8 days after primary treatment. No tumors were seen in 4 rats in which citrus oil applications were begun 18 days after primary treatment with DMBA. Discrepancies between text and tables in this publication, however, raise questions as to its reliability. Citrus oil alone did not induce any tumors but was very irritating to the skin, producing ulcers in both species.

Two investigators reported the absence of morphologically transformed colonies in cell transformation systems treated with limonene. Pienta (1980) reported negative results with limonene at concentrations up to 10 µg/ml in a hamster embryo cell transformation system without added metabolic activation. Negative findings were also observed by Traul and coworkers (1981) with reagent grade limonene (15 µg/ml) in an in vitro assay with Rauscher murine leukemia virus-infected F344 rat embryo cells.

Traul and associates (1981) also utilized this in vitro morphological transformation assay to study tumor promotion. They reported that cultures of Rauscher murine leukemia virus-infected F344 rat embryo cells treated with a subeffective dose of 3-methylcholanthrene (0.05 µg/ml), followed by regular application of reagent grade limonene (1.5 µg/ml) gave rise to foci of transformed cells. Transformation was confirmed by the growth of colonies of anchorage-independent cells in agarose. Cells treated with the subeffective dose of 3-methylcholanthrene alone or plus a higher concentration of limonene (15 µg/ml) and cells treated with the higher concentration (15 µg/ml) alone did not transform.

Driedger and Blumberg (1978) found that d-limonene did not mimic the phorbol esters (a potent class of tumor promoters for mouse skin) in their ability for causing loss of the large external transformation-sensitive glycoproteins (LETS) from the surface of chicken embryo fibroblasts (CEF), but did cause an increased rate of deoxyglucose transport (DG) by these cells. [The potencies of phorbol derivatives for promoting activities correlate with relative potencies for causing loss of LETS and stimulation of DG transport.] Addition of d-limonene (730 µM) to cultures of CEF 5 hours before the transport assay caused a maximum 2-fold increase in DG transport over levels in DMSO-treated controls. Driedger and Blumberg estimated that

d-limonene would be 197,000 times less potent as a promoting agent than the phorbol esters based on these results.

- Mutagenicity

Tests with d-limonene or its 1,2- and 8,9-epoxides indicated no mutagenic activity toward Salmonella typhimurium strains TA98, TA100, TA1535, TA1537 and TA1538. All three compounds were tested in the presence and in the absence of PCB-induced rat liver activation system at concentrations up to 0.1 µmol/plate; cytotoxic effects were noted at 1µmol/plate (Watabe and Hiratsuka, 1980; Watabe et al., 1980, 1981).

Florin and coworkers (1980) reported similar negative results for limonene in S. typhimurium TA98, TA100, TA1535 and TA1537 in the presence or absence of methylcholanthrene-induced rat liver homogenate at concentrations up to 0.3 µmol/plate. Concentrations equal to or greater than 3 µmol/plate were toxic.

Metabolic Characteristics

Schaefer and Schaefer (1982) reported cutaneous absorption of radiolabelled d-limonene, as a constituent of a foaming bath preparation, in mice. Pharmacokinetic measurements showed maximum blood levels occurred 10 minutes after the onset of absorption. Blood levels after 10 minutes were a direct function of the size of skin area involved.

Regan and Bjeldanes (1976) isolated 10 terpenoid metabolites in the urine of male Long-Evans rats administered 40 mg/kg d-limonene daily for 10 days by pharyngogastric intubation. Urine collection was started immediately after administration of the first dose and continued for 12 days (48 hours after the last dose). Ten urinary metabolites were isolated, seven of which were identified by chromatographic and spectral analysis. They included:

	% of total metabolites
p-mentha-2,8-dien-1-α-ol	} 37
p-mentha-2,8-dien-1-β-ol	
p-mentha-1,8-dien-6-α-ol	} 16.2
p-mentha-1,8-dien-6-β-ol	
p-mentha-2-ene-8,9-diol (uroterpenol)	5.1
p-mentha-1,8-dien-7-ol (perillyl alcohol)	0.4
4-isopropenyl-1-cyclohexene-1-carboxylic acid (perillic acid)	24.6

Among the 3 remaining metabolites (17.5%), two were identified as polyalcohols and one as a hydroxylated carboxylic acid. No d-limonene was detected.

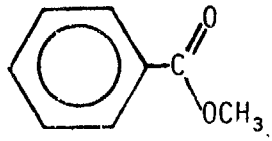
Rat liver microsomes were shown to convert d-limonene to the 1,2-epoxide, the 8,9-epoxide and the 8,9-glycol in the presence of NADPH. The 8,9-glycol was formed in the highest yield, the 1,2-epoxide in the next highest yield and the 8,9 epoxide was formed in low yield. The absence of the 1,2-glycol as a microsomal metabolite of d-limonene was attributed to the very low rate of microsomal hydrolysis of the 1,2-epoxide: about 1% of the

rate for the 8,9-epoxide. This biological selectivity in the microsomal oxidation of the d-limonene double bonds was attributed to a steric hindrance effect of the 1-methyl group in relation to the preferential microsomal epoxidation of the C8-double bond. The presence of the epoxide hydrolase inhibitor, 3,3,3-trichloropropene 1,2-oxide, completely inhibited microsomal hydrolysis of the 8,9-epoxide formed from d-limonene and resulted in its accumulation in the reaction medium without yielding any detectable amount of the 8,9-glycol (Watabe et al., 1981).

Regan et al. (1980) also reported that limonene-1,2-epoxide was not a major intermediate of limonene metabolism in the rat.

Monitoring and Detection

An alternative procedure to using liquid/liquid extraction to detect unmetabolized dipentene in blood or saliva samples is static or dynamic headspace analysis. Use of this technique may eliminate some interference as well as improve detection limits which are estimated to be 10 µg/L (Zlatkis et al., 1971, 1974; Miyashita et al., 1980).

Simulant:	Methyl Benzoate; Benzoic Acid, methyl ester
Formula:	
CAS Reg. No.:	93-58-3
Molecular Weight:	136.15
Chemical State (20°C):	colorless liquid
Liquid Density (g/cc):	1.0888
Vapor Density (compared to air):	4.68
Freezing/Melting Point (°C):	-12.3°
Boiling Point (°C):	199.6°
Flash Point (°C):	82.2°
Vapor Pressure (mm Hg at 20°C)	0.25 (Lyman et al., 1982, Chap. 14, method 2)
Volatility (mg/m^3):	1.9×10^3
Viscosity (cp at 20°C):	2.8
Odor:	pleasant, fruity odor
Action on Metals or Other Materials:	May soften or solubilize certain polymers; will act as a plasticizer and swell or spot various polymers, but effect should be reversible with no permanent or severe damage; no action on iron or mild steel.
Reference Source(s):	Furia and Bellanca (1975), Clayton and Clayton (1981); Lyman et al. (1982).

METHYL BENZOATE (Supplement)

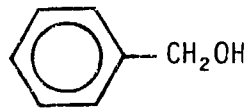
Potential Health Effects

Animal Studies

Pinching and Doving (1974) noted a conspicuous pattern of morphological changes (darkening and shrinkage of cell bodies) in the mitral cells of the olfactory bulb in Wistar rats continuously exposed by inhalation to an ambient concentration of 3.1×10^{-6} M methyl benzoate for up to 9 weeks beginning at two weeks of age. No manifestations of toxicity were reported and body weight gains were within normal limits.

Antibacterial Activity

Methyl benzoate at a 1:500 dilution in nutrient broth inhibited the growth of Bacillus subtilis ATCC 9524, Escherichia coli ATCC 11229, Staphylococcus aureus Ox-H (penicillin-sensitive) and Staphylococcus aureus ATCC 10390 (penicillin-resistant) after 24 hour incubations (Maruzzella and Bramnick, 1961).

Simulant:	Benzyl Alcohol
Formula:	
CAS Reg. No.:	100-51-6
Molecular Weight:	108.13
Chemical State (20°C):	colorless liquid
Liquid Density (g/cc):	d_4^{25} 1.0454
Vapor Density (compared to air):	3.72
Freezing/Melting Point (°C):	-15.3°
Boiling Point (°C):	205.3°
Flash Point (°C):	100.6° (open cup)
Vapor Pressure (mm Hg at 20°C)	0.033 (Lyman et al., 1982, Chap. 14, method 2).
Volatility (mg/m^3):	2.0×10^2
Viscosity (cp at 20°C)::	12.5 (Lyman et al., 1982, Chap. 22, method 3).
Odor:	pleasant, fruity odor
Action on Metals or Other Materials:	Will attack some plastics; leaches unreactive accelerators or their reaction products from rubber
Reference Source(s):	Furia and Bellanca (1975); Mellan (1970); MCA (1972); Clayton and Clayton (1981); Lyman et al. (1982); CHRIS (1974); Lachman et al. (1963).

BENZYL ALCOHOL (Supplement)

Potential Health Effects

Human Data

- Anesthetic Effects

A number of early studies reported the effective use of benzyl alcohol as a local anesthetic. Although benzyl alcohol is no longer used for this purpose, it is important to note that no significant adverse effects were attributed to its use. For instance, Macht (1918a) cited more than 30 cases in which 1-3% benzyl alcohol was used as an effective local anesthetic in a variety of surgical procedures with no apparent adverse effects.

Another early study reported the use of a benzyl alcohol-paraldehyde solution for relief of labor pain. The anesthetic, administered rectally, contained 1.5 ml benzyl alcohol and approximately 0.27 ml paraldehyde. Among the 611 women, complete relief from pain was experienced in 89.7%, partial relief in 2.6% and no relief in 7.7%. No apparent side effects such as nausea or vomiting were noted and no adverse effects on the heart, kidney, liver, lungs or respiratory center were evident (Kane and Roth, 1936).

Tainter and coworkers (1937) did not find benzyl alcohol to be as effective an anesthetic as the above studies. When a solution of 50% benzyl alcohol was applied to the mouth or gums of 61 individuals for approximately 2 minutes, complete anesthesia was experienced in 26 individuals (43%), partial anesthesia in 22 (36%) and no effect in 13 (21%). Among the 61 treated individuals, irritation or burning at the site of application was noted in 31%, hyperemia in 11% and sloughing in 4%, compared to averages of 15%, 8% and 0%, respectively, in aqueous controls. The benzyl alcohol solution was considered to be more caustic than desirable and elicited insufficient local anesthesia to be completely satisfactory as a local anesthetic for gums and oral mucosa.

Recent data suggest that undiluted benzyl alcohol is necessary for surface anesthesia. Aqueous solutions of benzyl alcohol, on the other hand, are not very efficient for surface anesthesia due to poor power of penetration into the tissues but are adequate for infiltration anesthesia (Federal Register, 1982).

Injection of benzyl alcohol-containing formulations into the broad ligament was found to relieve chronic pelvic pain in women with broad ligament neuritis. Injected formulations (4-6 ml) contained 5% benzyl alcohol and either ethyl-p-amino-benzoate in ether (A.B.A.®) or butyl-p-amino benzoate and procaine (Proctocaine®) in olive oil. Complete relief from pain was experienced by 25/50 (50%) of the women and considerable improvement was reported by 21/50 (42%).

Reich and coworkers (1943) reported complete relief from intractable pruritis vulvae with no adverse effects in 15 women treated with 1-2 subcutaneous injections of 2% procaine and 5% benzyl alcohol in olive, peanut or almond oil.

- Toxicity in Neonates

Although the above evidence suggests that benzyl alcohol can safely be used in adults, recent reports suggest that caution should be taken in exposing pre-term neonates to large doses of benzyl alcohol. Two separate medical centers reported 16 fatalities among pre-term neonates, all of which weighed less than 1,500 g., apparently resulting from the use of bacteriostatic normal saline containing 0.9% benzyl alcohol. The bacteriostatic saline was used during catheter placement, or for flushing central intravascular catheters after blood sampling, to dilute medications, etc. (Brown et al., 1982; Gershanik et al., 1981). The clinical picture was one of severe metabolic acidosis unresponsive to treatment with symptoms resembling progressive encephalopathy. Daily doses of benzyl alcohol were estimated at 130-405 mg/kg/day (avg. 191 mg/kg/day). Toxic symptoms included progressive metabolic acidosis, central nervous system depression, respiratory distress progressing to gasping respiration, hypotension, renal failure, seizures and intracranial hemorrhage (in some cases) and cardiovascular collapse preceding death. Urine samples from all six infants in one hospital revealed the presence of unmetabolized benzyl alcohol. Retrospective analyses of urine samples from 5 infants in the other facility showed benzoate levels of 4.4-16.1 mg/mg creatinine, and hippurate levels of 7.4-38.3 mg/mg creatinine (normal values are zero to trace amounts); serum benzoic acid levels were 8.4-28.7 mEq/L (normal value is 0). Brown and associates (1982) suggested that the large quantities of benzoic acid exceeded the capacity of the immature liver for detoxification, causing accumulation in the serum, leading to metabolic acidosis. The cause of the neurological symptoms was not clear, but was presumed to be due to the toxicity of benzyl alcohol or one of its metabolites.

On the basis of the evidence from these two reports, the Food and Drug Administration (FDA) (1982) recommended that benzyl alcohol not be used in solutions to flush intravascular catheters or in bacteriostatic water to dilute or reconstitute medications for newborns. However, both the FDA (1982) and the Center for Disease Control (1982) noted that, although all affected infants had biochemical evidence of benzyl alcohol toxicity, caution

should be taken in attributing the illness or death of individual infants to benzyl alcohol toxicity, since: 1) many of the clinical features noted in these cases are found in newborns seriously ill from other causes; 2) the affected infants had serious underlying diseases, weighed less than 1,500 g, were ventilator dependent and required at least one central catheter and frequent blood gas analysis; and 3) the newborns most likely to receive large volumes of flush solutions relative to body weight, would be the very small, very sick premature infants already at a high risk of mortality. The FDA (1982) also noted that no cases of a similar toxic syndrome have been reported in older infants, children or adults.

In another study, Bowen et al. (1975) noted no apparent correlation between plasma benzyl alcohol levels in hemodialysis patients and clinical symptoms. Plasma samples in 39 of 43 patients contained 5 to 500 µg benzyl alcohol/10 ml plasma prior to their hemodialysis treatment. Dialysis patients are routinely given heparin solutions containing benzyl alcohol prior to disconnection from the dialyzer.

- Skin Irritation

Benzyl alcohol was reported to be mildly irritating in a patch test with human volunteers in which 0.5 ml of solution (32% benzyl alcohol in acetone) was applied to the skin of the back and covered for 48 hours (Motoyoshi et al., 1979).

- Hematological Effects In Vitro

Benzyl alcohol was shown to cause a hemolytic effect with cultured human erythrocytes which was time, temperature and concentration dependent and appeared to result from the binding of the alcohol to the erythrocyte membrane. The minimum effective dose was 80 mM benzyl alcohol, while 100 mM was sufficient to produce 50% hemolysis at 37°C after 60 minutes (Ohmiya and Nakai, 1978).

Seeman (1972) reported that local anesthetic concentrations of benzyl alcohol actually decreased hypotonic hemolysis of human erythrocytes and caused increased hemolysis only at much higher concentrations. The protective effect was attributed to expansion and fluidization of the membrane.

Benzyl alcohol was also found to markedly decrease the intensity and duration of ADP-induced platelet aggregation following addition of 0.1, 0.5 or 1.0% benzyl alcohol to platelet rich human plasma; the inhibition was directly related to alcohol concentration. Benzyl alcohol also diminished the adhesiveness of platelets to glass (Zweifler and Sanbar, 1969).

Atkinson and associates (1976) noted a significant time- and dose-dependent increase in intracellular cAMP levels in several different cell types, including human peripheral blood lymphocytes, when exposed in vitro to 0.015-0.30% benzyl alcohol in heparin solutions. Enhanced cAMP levels were measurable within 2 minutes, usually peaked between 5 and 10 minutes and generally decreased to normal by 60 minutes. Heparin solutions without benzyl alcohol did not significantly increase the levels of cAMP. Concentrations of 0.5% benzyl alcohol or greater were cytotoxic and inhibited

the response. Benzyl alcohol also induced a significant increase in cAMP levels in human granulocytes, platelets and rabbit alveolar macrophages; however, the response was never as great as that observed in the lymphocytes (2-fold increases compared to up to 5-fold increases). It was suggested that the alcohol in some way perturbs the plasma membrane, thereby activating (possibly non-specifically) a membrane-bound cyclase.

Animal Studies

- Acute Toxicity

The Food and Drug Administration's Bureau of Veterinary Medicine recently issued warnings concerning possible adverse effects in a number of domestic animals attributed to large volume parenterals preserved with benzyl alcohol. Although these large volume parenterals were usually administered to animals already severely ill, with a much greater risk of death, there were also some reports of adverse effects and deaths among younger animals treated for dehydration. Cases of reactions in dogs, cats, calves and a colt were reported and included unexpected worsening of the animal's condition, development of salivation, hyperactivity and/or convulsions, usually leading to death. Investigation of this apparent problem is ongoing (Food Chemical News Guide, 1982).

- Diuretic Effects

Gruber (1924, 1925) reported a marked acceleration in the rate of excretion of urine in dogs and rabbits given intraperitoneal or intramuscular injections of benzyl alcohol. The rate of urine flow was increased an average of 171% in 18 rabbits and 4 dogs given 1-5 ml pure benzyl alcohol by intraperitoneal injection. Similarly, 1 ml of benzyl alcohol administered intramuscularly to rabbits caused an increase in flow from 1 drop/3 min. to 2 drops/min. The average latent period was approximately 7 minutes. The results obtained after intravenous injection were inconsistent and the mechanism behind the diuretic effect was not determined.

- Central Nervous System Effects

Benzyl alcohol had a marked effect on the peripheral motor branches of the facial nerve of the cat when injected subcutaneously at sites in front and below the external auditory meatus. Complete temporary paralysis of the obicularis oculi muscle (controls closure of the eyelids), lasting an average of 15 days, occurred in 18 trials involving 1-3 ml injections of 10% benzyl alcohol in sweet almond oil. In cases in which paralysis persisted for 10 or more days, all, or nearly all, of the nerve fibers in the facial branches to the orbicularis oculi were found to be in a state of degeneration. Return of function (eventually complete in all cases) was dependent upon regeneration. In all cases the maximal effect was elicited at the time of injection and no signs of prolonged functional block and subsequent degeneration were noted (Duncan and Jarvis, 1943).

An immediate local anesthetic effect of the whole leg was induced in rats following periarticular injection of 0.1 ml of 20% benzyl alcohol in 70% polyethylene glycol (PEG). The persistence of residual incomplete anesthesia for up to a week suggested the presence of lesions in the involved nervous

structures. No effect was induced with 10% benzyl alcohol. Intraperitoneal injection of 0.5 ml 20% benzyl alcohol in 70% PEG or of 5 ml of 2% benzyl alcohol caused complete general anesthesia within 2-5 minutes. Similar complete but very temporary narcosis was produced in a dog after intravenous injection of 0.2 ml/kg benzyl alcohol (Eichbaum and Yasaka, 1976).

Solutions of 2-4% benzyl alcohol were reported to be effective spinal anesthetics in dogs, producing anesthesia of the posterior part of the body when injected into the subdural spaces. A severe fall in blood pressure, depression and, in some cases, respiratory failure occurred when application was to the fourth ventricle. Dissolving the benzyl alcohol in olive oil was effective in reducing the diffusion of the alcohol to the upper part of the spinal cord (Voegtlin and Livingston, 1919).

A dose of 3 mmole/kg (approximately 324 mg/kg) benzyl alcohol was necessary to produce ataxia in rats when administered by single intraperitoneal injection. Ataxia in this case was defined as pronounced impairment of gait and motor incoordination with the abdomen and pelvis still elevated (McCreery and Hunt, 1978).

- Circulatory and Respiratory Effects

A drop in arterial blood pressure in dogs similar to that observed by Macht (1918a,b) was reported by Gruber (1923b) following intravenous injection of 3 ml of a 10% benzyl alcohol emulsion. Unlike Macht (1918a,b), however, Gruber also noted an increase in the rate of respiration and a decrease in the depth of respiration at this dose level, while larger doses caused paralysis of the respiratory center. Also in conflict with Macht (1918a,b), Gruber (1923a,b) found that cardiac paralysis preceded respiratory paralysis following administration of large fatal doses of benzyl alcohol.

Similar to other studies, Gruber (1923a) noted no adverse effects in either anesthetized or unanesthetized dogs following oral administration of benzyl alcohol. No drop in blood pressure was apparent after administration by stomach tube of 0.1-1.0 ml/kg benzyl alcohol. Although moderately large doses (0.2 ml/kg) did cause a rise in blood pressure, this effect was attributed to restlessness of the animal resulting from cathartic and emetic effects of the treatment rather than direct action of the benzyl alcohol on the circulatory system. No alteration in pulse rate was observed with doses of 2.0, 4.2 or 5.4 ml pure benzyl alcohol via stomach tube (approximately 0.1-0.2 ml/kg). The emetic effect produced by doses of 2.5-10.8 ml benzyl alcohol was apparently caused by local irritation of the gastric and intestinal mucosa, rather than excitation of the vomiting center. This was apparently also true of the cathartic effect, since the time interval between exposure and effect was too short to be due to relaxation of the smooth muscle lining of the gastrointestinal tract. Subcutaneous or intramuscular administration of similar doses of benzyl alcohol did not result in these effects.

- Antiarrhythmic/Inotropic Effects

Several recent studies report an apparent antiarrhythmic effect produced by benzyl alcohol in several mammalian species. Intravenous injection of

0.1-0.4 ml/kg of 4% benzyl alcohol induced an effective antiarrhythmic action within 30-60 seconds in dogs with several forms of spontaneous or drug-induced arrhythmias. In cases where normalization of the rhythm appeared to last only a few minutes, administration of a second, identical dose generally produced a permanent return to normal. Similarly, a prompt antiarrhythmic effect was elicited in rats injected with 0.2-0.6 ml/kg of 1-2% benzyl alcohol. Rapid intravenous infusion of a 20% benzyl alcohol solution in 70% PEG, as a bolus, caused temporary apnea, and in some cases, an irreversible respiratory standstill and cardiac arrest.

Although the exact mechanism of the antiarrhythmic effect was not certain, several possibilities were suggested, including a benzyl alcohol-induced lengthening of the effective refractory period. The local or general anesthetic activity of benzyl alcohol could also have been a factor. Evidence also indicates that benzyl alcohol acts directly upon the myocardium which is exposed to high concentrations of the compound immediately after intravenous injection (Eichbaum and Yasaka, 1976).

Another study by Yasaka and associates (1979a) showed that benzyl alcohol alone or in combination with PEG (20%BA:70%PEG) did produce a distinct lengthening of the effective refractory period (ERP) of isolated rabbit atria. The maximum effect was reached after 10-20 minutes and stabilized thereafter; this time requirement was apparently independent of concentration. The minimum effective concentration of either solution began at 10^{-4}M and the maximum effect was reached at 10^{-2}M. The maximum lengthening of the ERP was 40% of benzyl alcohol alone and 45% of the benzyl alcohol:PEG mixture. No significant variations in ERP were observed in atria not exposed to the benzyl alcohol, even after 60 minutes.

Yasaka and coworkers (1979b) also reported that benzyl alcohol alone or in combination with PEG produced a negative inotropic effect (decreased contractile force) on isolated rabbit atria; effective concentrations were 10^{-2} to 10^{-1}M benzyl alcohol alone or 10^{-2} to $5x10^{-1}$M PEG (70%) with 10^{-3} to $5x10^{-2}$M benzyl alcohol (20%). The time required for maximum effect varied from 15-30 seconds and was dependent upon concentration. Even at high concentrations resulting in an almost 100% decrease in contractile force, the atria returned to normal conditions of frequency and force of contraction within 10 minutes after washing. The negative inotropic effect of benzyl alcohol was attributed to an inhibition of calcium uptake by lipoproteic membranes.

Eichbaum and Yasaka (1976) also noted that injections of high doses of benzyl alcohol alone or in combination with PEG (20% and 70%, respectively) caused a strong intravascular hemolytic effect in dogs and rats. The hemolytic end titer (100% hemolysis) was determined to be 2.5 mg/ml benzyl alcohol.

- Subchronic Toxicity

Long-term oral administration of 300 mg/kg benzyl alcohol by gastric intubation to adult female rats for 87 days produced no adverse effects on body weight or hematology. No abnormalities were noted in microscopic examination of organ tissues (Laboratoire Pharmacotechnique Dubois and Vincent, 1964).

- Mutagenic Effects

A negative mutagenic response was observed with benzyl alcohol (3 µmol/plate) in the Ames assay spot tests with Salmonella typhimurium TA98, TA100, TA1535 and TA1537, both in the presence and absence of liver microsomal activation from Aroclor® 1254-induced rats (Florin et al., 1980).

- Reproductive Effects

Injections of 0.01-0.02 ml undiluted benzyl alcohol into the yolk of fertilized chick eggs either before incubation or during the first seven days of incubation caused various embryonic abnormalities including meningoceles, limb deformities, beak defects (i.e., arched upper beaks), localized blebs (flaccid vesicles) and generalized edema. Few of the benzyl alcohol-injected embryos survived to Day 11 of incubation (Duraiswami, 1954). The high incidence of lethality as well as the lack of anatomic and physiologic maternal-fetal relationships and the resultant ultra-sensitivity of this test system render it unsuitable for assessing potential teratogenic risk in humans.

Macmillan (1973) reported that benzyl alcohol infused into the uterus as an acidified buffered 5% emulsion caused a shortening of the estrus cycle in normal mature dairy cows; infusion volumes ranged from 5-40 ml (0.5-2.0 ml benzyl alcohol). In a similar study, Smith and coworkers (1979) found that benzyl alcohol could induce either a luteolytic reaction or a luteotrophic reaction when administered to non-lactating cows by a single intrauterine injection of 5 ml of a 20% solution at various times during the estrus cycle. Treatment during the early luteal phase of the cycle (days 4-7) caused a premature decline in progesterone levels and an average cycle length of 16 days; treatment mid-cycle (days 8-11) had little effect; and treatment late in the cycle (days 12-20) prolonged the luteal phase, with average cycle lengths of 25-28 days. Smith suggested that the ability to induce a luteolytic response (early in the cycle) and a luteotrophic response (late in the cycle) suggests that benzyl alcohol may alter prostaglandin synthesis and/or release by interacting with the inhibitor of prostaglandin biosynthesis present in the bovine endometrium.

- Bacteriostatic/Bactericidal Effects

A number of older studies reported the bacteriostatic/bactericidal activity of benzyl alcohol at concentrations of 1% or less against a variety of microbial species (Macht and Nelson, 1981; Macht and Hill, 1923; Gershenfeld, 1952; Nishimura et al., 1950; Schaffer and Tilley, 1927; Jurgens, 1976; Morton 1976).

Metabolic Characteristics

Several older studies support the current consensus that benzyl alcohol is rapidly oxidized to benzoic acid, conjugated with glycine and excreted as hippuric acid in both man and animals. Snapper and coworkers (1924) found that within 6 hours after ingestion of 1.5-2 g benzyl alcohol, humans on a pure milk and flour diet excreted 74-88% of the dose as hippuric acid. Diack and Lewis (1928) reported that oxidation of benzyl alcohol in the rabbit was

quite rapid following its administration by stomach tube. Urinary excretion as hippuric acid accounted for 65.7% and 72.8% of the dose at 6 and 24 hours, respectively.

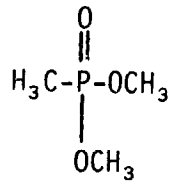
Stekol (1939) found hippuric acid but little or no benzyl mercapturic acid in the urine of rats and/or rabbits given subcutaneous injection of benzyl alcohol (rabbits: 1 g in 3 portions, 2 hours apart; rats: 0.5 g/kg). Administration of 250 mg/kg benzyl alcohol by stomach tube to rabbits yielded similar findings (Bray et al., 1958).

SIMULANT CANDIDATES

The available information on two volatile, one intermediate, five low and three nonvolatile candidate simulants is presented in this section.

The proposed candidate simulants include:

Volatile candidates:	Dimethyl methylphosphonate
	n-Dodecanethiol
Intermediate volatility candidate:	Methyl salicylate
Low volatility candidates:	Butyl salicylate
	N,N-Diethyl-m-toluamide
	Diethyl sebacate
	Dibenzyl ether
	Isoamyl benzoate
Non-volatile candidates:	Anisyl phenylacetate
	n-Octadecanethiol
	Phenylethyl phenylacetate

Simulant:	Dimethyl Methylphosphonate
Formula:	
CAS Reg. No.:	756-79-6
Molecular Weight:	124.08
Chemical State (20°C):	liquid
Liquid Density (g/cc):	d_4^{20} 1.145
Vapor Density (compared to air):	4.3 (Lyman et al., 1982)
Freezing/Melting Point (°C):	
Boiling Point (°C):	181°
Flash Point (°C):	43°
Vapor Pressure (mm Hg at 20°):	0.61 (Lyman et al., 1982)
Volatility (mg/m^3):	4100 (Lyman et al., 1982)
Viscosity (cp at 20°C):	4.1 (Lyman et al., 1982)
Odor:	
Action on Metals or Other Materials:	
Reference Source(s):	RTECS (1980); Aldrich (1980); Lyman et al. (1982)

DIMETHYL METHYLPHOSPHONATE

Potential Health Effects

Human Data

No information on the effects of dimethyl methylphosphonate (DMMP) exposure in humans was found.

Animal Studies

Hollingshaus and associates (1981) reported an oral LD_{50} value of greater than 150 mg/kg for dimethyl methylphosphonate administered in corn oil to fasted female Sprague Dawley rats. The administered compound was greater than 99% pure. Survivors were kept under observation for 25 days; no delayed deaths occurred.

These investigators also reported that 50 mg/kg dimethyl methylphosphonate was the lowest dose that produced any visually detectable ataxia in adult White Leghorn hens administered the compound daily for 10 days by intraperitoneal injection. Birds were examined daily for 60 days for clinical signs of ataxia, but no delayed neurotoxic activity was observed.

DMMP is currently under test for carcinogenic activity in B6C3F1 mice and Fischer 344 rats by the gavage route. The study is being conducted under the auspices of the National Toxicology Program. Preliminary 90-day subchronic studies have been completed. B6C3F1 mice of both sexes were given DMMP (>98% pure, in corn oil) by daily oral gavage five days per week for the 3 month period. Dosage levels were 0, 250, 500, 1000, 2000, 4000 and 8000 mg/kg body weight. High mortality (≥90%) was noted at the 4000 and 8000 mg/kg dosage levels. No significant effect on relative weight gain and generally few signs of toxicity were seen in mice that died or were moribund, nor could the high mortality be explained by histopathological findings. All mice (both sexes) in the 2000 mg/kg treatment group survived and had no microscopic changes that could be attributed to treatment with DMMP. The maximum tolerated dose of DMMP in both sexes was estimated to be 2000 mg/kg (Litton Bionetics, Inc., 1979a).

In the subchronic study conducted with Fischer 344 rats, test animals were administered DMMP by gavage, 5 days per week for 13 weeks. Dosage levels were 0, 250, 500, 1000, 2000 and 4000 mg/kg body weight. All rats in the highest dose group died within the first week of compound administration. Nine of twenty rats in the 2000 mg/kg treatment group died during the study (one death was attributed to gavage trauma). No compound-related deaths occurred below 2000 mg/kg. No significant signs of toxicity or changes in body weight were noted. Increased liver to body weight ratios were recorded at necropsy for the 2000 mg/kg treatment group (both sexes). Histopathological examination revealed lesions in kidneys (nephropathy), salivary glands (possibly attributable to concurrent sialodacryoadenitis virus infection) and testes. Additional information on testicular lesions was not provided. The maximum tolerated dose of DMMP in both sexes of F344 rats was estimated to be 1000 mg/kg (Litton Bionetics, Inc., 1981).

An earlier 3 month gavage study conducted with DMMP in rats (Litton Bionetics, Inc., 1979b) revealed changes in the mandibular salivary glands at the 4000 and 8000 mg/kg treatment level, some nephrosis in kidneys at 8000 mg/kg, and atrophy of the testes was found in at least one of three rats each in the 250, 500, 1000 and 2000 mg/kg dose groups. Degeneration and atrophy of the germinal epithelial cells were the salient histological features. Epididymal changes were seen in rats at the 4000 and 8000 mg/kg levels. The significance of findings in this study were questioned, however, due to an excessive number of deaths due to esophageal puncture at the lower dosage levels.

DMMP reportedly induced no mutagenic response in four strains of Salmonella typhimurium in a standard Ames assay (Dr. June Dunnick, NIEHS, N. Carolina; personal communication, September, 1982).

Monitoring and Detection

It is unknown whether DMMP is metabolized in man. If DMMP is not metabolized, an appropriate analytical technique would include liquid/liquid extraction and gas chromatography with flame photometric detection (GC/FPD). An aliquot of the urine sample is extracted into methylene chloride. This extract is then dried through anhydrous sodium sulfate and concentrated using a Koderna-Danish apparatus. The extract is chromatographed on 10% Carbowax 20 M coated on 100/120 mesh Supelcoport packed in a 10 feet by 2 mm internal diameter column. The gas chromatographic conditions necessary for resolution of the DMMP from interferences will need to be optimized. The flame photometric detector is operated in the phosphorous mode. The detection limit for DMMP is estimated to be 25 picograms injected on a column (Fasano et al., 1982).

Simulant:	n-Dodecanethiol
Formula:	$C_{12}H_{25}SH$
CAS Reg. No.:	122-55-0
Molecular Weight:	202.41
Chemical State (20°C):	white to yellow colored liquid
Liquid Density (g/cc):	d_{20}^{20} 0.8450
Vapor Density (compared to air):	7.02 (Lyman et al., 1982)
Freezing/Melting Point (°C):	(18°) (-7°)
Boiling Point (°C):	142.5° (266-283°)
Flash Point (°C):	128° (open cup) (Clayton and Clayton, 1981); 87° (Aldrich, 1980)
Vapor Pressure (mm Hg at 20°C):	5.3 (Lyman et al., 1982); 2.5 at 25° (NIOSH,1978b)
Volatility (mg/m^3):	58,000 (Lyman et al., 1982)
Viscosity (cp at 20°C):	2.2 (Lyman et al., 1982)
Odor:	
Action on Metals or Other Materials:	May react with some rubbers, but effect should not be too severe (K. Sidman, Arthur D. Little, Inc., personal communication)
Reference Source(s):	Clayton and Clayton (1981); Sax (1979); Lyman et al. (1982); Aldrich (1980).

n-DODECANETHIOL

n-Dodecanethiol is a white to yellow colored liquid with a mild characteristic thiol odor. It is used in the chemical synthesis of pharmaceuticals, insecticides, fungicides, non-ionic detergents and bacteriocides, in synthetic rubber processing and in froth flotation agents for metal refining, particularly for copper ores. An estimated 21,150 workers are exposed to dodecanethiol in the U.S. (NIOSH, 1978b). The recommended ceiling limit for any 15 minute exposure has been established at 4.1 mg/m^3 or approximately 0.5 ppm (NIOSH, 1978b).

Potential Health Effects

Human Data

Thiols, in general, act as weak acids with their chemical reactivity essentially due to the sulfhydryl moiety. The primary biological target of inhaled thiol vapors is the central nervous system (the neurons). All thiols have a characteristic obnoxious odor that constitutes a nuisance at concentrations often far lower than those which cause symptoms of toxicity (ppb to ppm levels). In general, the lower molecular weight compounds have a more obnoxious odor than the higher molecular weight thiols. The thiols are absorbed through the skin upon contact and may cause dermal irritation; dermal toxicity may be of more importance in the higher molecular weight thiols, i.e. >6 carbons.

- Skin Sensitization

Positive sensitization responses were noted in closed patch tests in 15/45 (33%) individuals with shoe contact dermatitis when tested with 0.1% dodecanethiol (in toluol), a formulation used in the Spanish shoe industry. An additional 8/45 subjects (18%) exhibited an irritant response, while the remaining 22/45 (49%) experienced no reaction. Positive responses were also observed in 9/45 (20%) of the subjects when patch tests were conducted with Neoprene® ACM resin, a glue containing dodecanethiol which is used in the shoe industry. Among 123 healthy individuals, irritant reactions were experienced by 12/123 (10%), 28/123 (23%) and 66/123 (54%) individuals in closed patch tests with 0.1, 0.5 or 1.0% dodecanethiol in toluol. No sensitization responses were seen. Negative results were also noted in 51 control subjects in an open patch test using these same three concentrations of dodecanethiol (Grimalt and Romaguera, 1975).

- Mutagenicity

Significant increases in the frequency of chromosomal aberrations in peripheral blood lymphocytes were noted in 11 workers employed in a factory producing polychloroprene latex used in the manufacture of footwear. The employees were exposed to vapors containing a mixture of 2-7 mg/m^3 chloroprene, 1-2.5 mg/m^3 dodecanethiol and 4-10 mg/m^3 ammonia for an unspecified length of time. The majority of aberrations were chromatid breaks. Chromosome breaks were also noted, but to a lesser degree, while rings, dicentrics and exchange figures were not observed (Bagramyan et al., 1976; Bagramyan and Babaian, 1974). The contribution of dodecanethiol to the observed response is difficult to assess in the absence of additional data.

- Carcinogenicity/Teratogenicity/Chronic Effects

No data were found concerning potential carcinogenic, teratogenic or long-term effects in humans exposed to dodecanethiol.

Animal Studies

- Acute Toxicity

The intragastric LD_{50} of dodecanethiol in mice was reported as 4.225 (3.069-5.381) g/kg, while no deaths occurred among rats dosed with 7 g/kg (Gizhlaryan, 1966). The intravenous LD_{50} in mice was reported as >0.316 g/kg (NIOSH, 1978b). Gizhlaryan (1966) found that 3.4 ± 0.1 mg/L dodecanethiol applied to the skin of rats or mice caused marked local effects and "general poisoning." Other data from this study indicated that, in general, higher molecular weight thiols had a lower acute toxicity than lower molecular weight thiols.

- Subchronic Toxicity - Inhalation Effects

No signs of toxicity were noted in 4 rats exposed to a "nearly saturated atmosphere" of dodecanethiol for up to 6 hr/day, 5 days/wk for 4 weeks (total of 20 exposures). Microscopic examinations revealed no signs of abnormalities (Gage, 1970).

In a similar experiment, rats were exposed to dodecanethiol-saturated air (3,400 mg/m^3 or 411 ppm), 4 times/wk for 2 months (length of daily exposure was not specified). No changes were noted in body weight, oxygen consumption, ability of the central nervous system to summate threshold pulses, blood catalase level, erythrocyte count, sulfhydryl content in the hemolysate or liver function. After 5.5 months of exposure, a suppression in body weight gain was accompanied by slight changes in oxygen uptake by red blood cells and oxygen usage by the tissues. A slightly increased leukocytosis, a 50% decrease in function of the adrenals and a reduced liver function were also noted, along with small increases in the sulfhydryl content of the liver, spleen, brain and kidney, but not the blood. There was no change in the ratios of organ weights to body weight. Microscopic examination revealed vascular congestion in all organs, hemorrhages in the lungs and adrenal medulla, mild bronchitis, slight inflammation of renal tubules, myocardial fibrosis, slight fatty infiltration of the liver, depletion of lipid in the adrenal cortex and slight edema of the brain. The authors concluded that dodecanethiol was of low toxicity via the inhalation route and would present only a slight hazard to industrial workers. However, the possibility of low-level chronic intoxication in workers was not completely eliminated (Gizhlaryan, 1966).

- Skin Sensitization/Epidermal Hyperplasia

Dodecanethiol was described as having an intense contact sensitizing ability in guinea pigs following ten daily applications of 0.2 ml of a 20% solution (0.04 ml/day) in acetone to the depilated flank. Approximately 50% of the animals developed dermatitis after a single application of dodecanethiol. When animals were painted on the opposite flank with dodecanethiol one month later, signs of sensitivity were apparent within 24 hours, compared

to 3-5 days in controls; the duration of the dermatitis was not stated (Cirstea, 1972).

Solutions of dodecanethiol in ether (0.2 ml) applied every other day for six days (3 mg) to the shaved backs of albino mice caused elongated and swollen hair follicles, and increased weight, cell thickness, and cholesterol levels of the epidermis. Despite this epidermal hyperplasia, the levels of Δ^7-cholesterol in the epidermis and the histopathology of the sebaceous glands were normal for both the above dosage and doses of 0.2 ml undiluted dodecanethiol (500 mg) (Brookes et al., 1957).

Although there is no evidence suggesting that the thiols affect human skin after single or repeated dermal exposure, these animal data for dodecanethiol along with data for other thiols suggest that a delayed dermatitis may be possible (NIOSH, 1978b).

- Mutagenicity

Increased frequencies of chromosomal aberrations were noted in rat bone marrow cells following daily inhalation of a mixture of 1.96 mg/m^3 chloroprene, 5.02 mg/m^3 dodecanethiol and 19.8 mg/m^3 ammonia, three components of polychloroprene latexes. After a 24 hour exposure, the frequency of aberrations increased to 8.8% from a control value of 5.5%. After weekly exposure for up to 4 months, the frequency of aberrations in treated animals was 11.1% above that of controls; the exact length of each exposure period was not stated (Bagramyan and Babaian, 1974).

Another study by Bagramyan and associates (1976) suggested similar results. Two different secondary sources which cited this Armenian study, however, provided slightly different data. NIOSH (1978b) reported that results from this study showed a frequency of chromosomal aberrations (consisting mainly of chromosomal fragments) in treated rats of 10.1% compared to 5.3% in controls, following 120 days of exposure to a mixture of 0.89 ± 0.9 mg/m^3 chloroprene, 0.12 ± 0.03 mg/m^3 dodecanethiol and 2.07 ± 0.27 mg/m^3 ammonia. A Chemical Abstract citation (085/172283R) for this study noted the same frequencies of chromosomal aberrations in control and treated rats; however, concentrations of the mixture components were given as 1.96 mg/m^3, 5.02 mg/m^3 and 19.8 mg/m^3 for chloroprene, dodecanethiol and ammonia, respectively (the length of exposure and duration of treatment were not given). This source also called the aberrations chromosomal rearrangements and indicated that they were found in the brain cells of treated rats. In either case, dodecanethiol was implicated as a possible mutagen.

- Carcinogenicity/Teratogenicity/Chronic Effects

No data were available concerning potential carcinogenic, teratogenic or long-term effects in animals following exposure to dodecanethiol.

Metabolic Characteristics

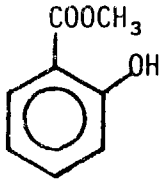
Although no specific information concerning the metabolic fate of dodecanethiol was found, NIOSH (1978b) proposed the following scheme for alkane thiols, in general. The sulfur atom is metabolized by oxidation and excreted, for the most part, as urinary inorganic sulfate. In addition,

methylation of the thiol followed by oxidation leads to excretions of some of the sulfur as the sulfone of the methylated thiol. The latter pathway appears to be more important for the higher molecular weight thiols. The sulfur atom is apparently not incorporated into cysteine or methionine sulfur in mammals. The thiols do not appear to be oxidized to disulfides in vivo, although this conversion takes place readily in vitro. It is possible that the thiols are maintained in the reduced state in vivo.

Monitoring and Detection

An excellent review of the information available on thiols was published by NIOSH (1978b). A NIOSH method is available for the analysis of butanethiol in air samples (NIOSH, 1978a). The traditional method for detection of thiols in biological fluids involves the use of Ellman's reagent (Burg et al., 1982). The analysis of such organosulfur compounds has also been reported from waste waters (Jenkins et al., 1980). The method uses gas chromatography coupled with a sulfur specific flame photometric detector, with sensitivity in the ppb (ml odorant/ml air) range.

Limited information is available on the metabolism and bioanalysis of alkane thiols. The thiols would probably be methylated, followed by oxidation, with the major excretion product being the sulfone of the methylated thiol. Analytical methods would need to be developed for the analysis of the parent thiol or methylated sulfone metabolite in urine samples. Gas chromatographic or high performance liquid chromatographic techniques should be suitable for this purpose.

Simulant:	Methyl Salicylate
Formula:	
CAS Reg. No.:	119-36-8
Molecular Weight:	152.14
Chemical State (20°C):	colorless yellowish or reddish liquid
Liquid Density (g/cc):	d_4^{20} 1.1738
Vapor Density (compared to air):	5.24
Freezing/Melting Point (°C):	-8.6°
Boiling Point (°C):	220-224°
Flash Point (°C):	101.1°
Vapor Pressure (mm Hg at 20°C):	0.087 (Lyman et al., 1982)
Volatility (mg/m^3):	730 (Lyman et al., 1982)
Viscosity (cp at 20°C):	9.7 (Lyman et al., 1982)
Odor:	wintergreen
Action on Metals or Other Materials:	
Reference Source(s):	Stecher (1968); Sax (1979); RTECS (1980); Lyman et al. (1982); Dean (1979).

METHYL SALICYLATE

Methyl salicylate has the characteristic odor and taste of wintergreen. It is widely used in the perfume and food industries, as well as medicinally in the form of local analgesic or anti-inflammatory ointments or liniments (Collins et al., 1971). It was given GRAS status by the Flavor and Extract Manufacturers' Association (1965). The Food and Drug Administration proposed tolerances for methyl salicylate of 100 ppm in bakery goods, 300 ppm in candy, 70 ppm in carbonated beverages, 3300 ppm in chewing gum and 50 ppm in ice cream (Food Chemical News Guide, 1982). Methyl salicylate is also cleared for use in adhesives and as an antioxidant and stabilizer for semirigid and rigid acrylic and modified acrylic plastics (Food Chemical News Guide, 1982). Furia and Bellanca (1975) reported uses of 54 ppm in bakery goods, 840 ppm in candy, 59 ppm in non-alcoholic beverages, 8400 ppm in chewing gum, 27 ppm in ice cream and 200 ppm in syrups. The Eleventh Report of the Joint FAO/WHO Expert Committee on Food Additives (1968) reported an estimated acceptable daily intake for man of up to 500 µg/kg body weight.

Potential Health Effects

Human Data

- Acute Toxicity

Although methyl salicylate is considered safe for use as a flavoring agent in various foods when added in low concentrations, it has been found to be acutely toxic when ingested in relatively small but concentrated amounts. A dose of 30 ml concentrated methyl salicylate (~0.5 g/kg) may be fatal to adults, while as little as 4-10 ml may be fatal to infants or children, depending on the size and condition of the child (Stecher, 1968; Adams et al., 1957; Cann and Verhulst, 1958; Canselmo, 1948; Deichmann and Gerarde, 1969; Wade, 1977).

Symptoms of methyl salicylate poisoning are similar to those caused by other salicylates (i.e., sodium salicylate, acetylsalicylic acid) and may include nausea, vomiting, perspiration, marked thirst and dehydration, occasional diarrhea, acidosis, pulmonary edema, pneumonia, hyperpyrexia, hyperpnea, high blood pressure, increased heart rate, dimness of vision and excitation of the central nervous system. In severe cases, generalized convulsions and coma are followed by cardiovascular collapse and respiratory insufficiency leading to death within 12-36 hours after exposure (Adams et al., 1957; Stecher, 1968; Deichmann and Gerarde, 1969). In general, symptoms of salicylate poisoning become apparent with blood salicylate levels of approximately 25 mg/100 ml, severe intoxication in individuals with lower blood salicylate levels, however, is not uncommon (Cann and Verhulst, 1958; Deichmann and Gerarde, 1969).

Methyl salicylate poisoning is apparently due to the salicylate moiety, and not the methyl alcohol produced by hydrolysis of the ester in the stomach. Most clinical signs of methyl salicylate poisoning are attributable to changes in the acid-base balance and electrolyte structure of the plasma. Salicylate stimulation of the respiratory center produces hyperpnea and results in a CO_2 deficit in blood, decreased carbonic acid content and a rise

in blood pH (i.e., respiratory alkalosis). Renal compensation by increased bicarbonate excretion facilitates the development of acidosis. Another contributing factor to acidosis is a salicylate-induced change in carbohydrate metabolism which causes an abnormal production and accumulation of organic acids. The removal of these abnormal metabolic end-products results in the excretion of fixed base. Salicylates have been shown to inhibit the first two steps in the Kreb's tricarboxylic cycle, resulting in ketosis which may contribute to the acidosis. The diaphoresis and hyperpnea produced by the salicylate moiety cause water loss from the body, which is increased by coincident vomiting and diarrhea. This leads to body water deficit with impaired renal function and decreased salicylate excretion. Salicylate poisoning may also cause hypoprothrombinemia, leading to depression of plasma fibrinogen and widespread capillary damage (Cann and Verhulst, 1958; Adams et al., 1957). Hyperlactatemia and hyperkalemia were observed in patients who subsequently died from myocardial failure following accidental ingestion of ~30-90 ml of methyl salicylate. Autopsy revealed myofibrillar necrosis which was most marked in the subendocardial region of the left ventricle (Ojiambo, 1971b).

- Dermal Effects

Methyl salicylate is a strong dermal and mucous membrane irritant and is readily absorbed through the skin. Although it is considered to be too irritating for internal use, methyl salicylate has been frequently employed as a topical counterirritant, analgesic and/or anti-inflammatory agent. It is used both undiluted or in various ointments, liniments and lotions for relief of pain, stiffness and inflammation of sciatica and rheumatic conditions (Wade, 1977; Tilley, 1980; Deichmann and Gerarde, 1969; Davison et al., 1961). When applied to the skin, the resulting irritation reportedly interferes with the transmission of impulses from local pain fibers. Tilley (1980) urged that caution should be taken to avoid application to the eyes or mucous membranes because of potential severe irritation and to avoid application to irritated skin, wounds or large areas of the body because of potential toxicity resulting from systemic absorption.

Although Morgan (1968) reported sensitivity to methyl salicylate confirmed by patch tests in 2 patients, Epstein (1973) reported no irritation and no sensitization after application of methyl salicylate (8% in petrolatum) for 48 hours with occlusion.

- Hemolytic Effects In Vitro

Two studies reported significant hemolysis in human red blood cells incubated with methyl salicylate at concentrations as low as 0.004 ml (in 5 ml solution). The hemolytic effect was concentration- and time-dependent with maximum effects seen with 60 minutes exposure to 0.01 ml. Methyl salicylate appears to cause hemolysis, even at very low concentrations, by reducing the surface tension, resulting in damage to the erythrocyte membrane (Muragesh, 1981a). This was further substantiated by the effective and significant antagonism of the methyl salicylate-induced hemolysis by addition of a variety of drugs to the cell suspension; these included urethane, histamine acid phosphate, procaine hydrochloride, acetazolamide and

tetracycline hydrochloride. Hemolysis was decreased approximately 70% by the simultaneous addition of 1 x 10^{-3} M antagonist and 1 x 10^{-3} M methyl salicylate to the red blood cells or by the initial incubation of cells and antagonist, prior to addition of methyl salicylate. Although the exact mechanism of this protective effect is not known, it was suggested that complexes or interactions between the methyl salicylate and the drugs led to inactivation of the methyl salicylate, thus preventing the lowering of the surface tension and the resulting membrane damage (Muragesh, 1981b).

- Cytotoxicity

At concentrations of 1, 10 or 100 µg/ml, methyl salicylate was not cytotoxic to HeLa cell cultures (Silyanovska et al., 1968).

Animal Studies

- Acute and Subchronic Toxicity

LD_{50} values for a number of different species have been reported (Opdyke, 1978b; Stecher, 1968; Sax, 1979; RTECS, 1980) as follows:

Species	Oral LD_{50} (mg/kg)	Dermal LD_{50} (mg/kg)
mouse	1100	
rat	887, 1250	
guinea pig	700, 1060	
rabbit	1300, 2800	>5000
dog	2100	

Administration of 0.5 ml methyl salicylate by gavage caused slight redness and irritation of the stomach mucosa of rats (Strom and Jun, 1974). In another study, however, methyl salicylate was found to have markedly less acute gastric ulcerogenic activity compared to salicylic acid when administered orally to rats. Groups of 4-6 animals were given a 1 ml suspension of methyl salicylate in water, or the same dose of salicylic acid, followed by a brief exposure to the cold (1-15°C for 45 minutes) as a stress-sensitizing procedure. The number of gastric lesions was reduced from 4.8 ± 1.9 with salicylic acid to zero with methyl salicylate. This reduction in ulcerogenic activity was apparently not accompanied by any anti-inflammatory activity. In the same study, oral administration of methyl salicylate was also notably more effective than salicylic acid in significantly reducing fever induced in rats by subcutaneous injection of 2 g/kg dried Brewer's yeast in saline (Rainsford and Whitehouse, 1980; Whitehouse and Rainsford, 1980).

Administration of 0.6-4.7 g/kg methyl salicylate by intubation into the stomach and duodenum of 4 dogs caused nausea, vomiting, diarrhea, intense hyperpnea, excitation of the central nervous system and death in two animals at 8 and 18 hours, respectively. An increase in respiratory amplitude but no change in arterial pressure were noted when anesthetized dogs were given 0.6-5 g/kg methyl salicylate (Lacroix and Ferragne, 1964).

Ojiambo (1974), however, reported a drop in blood pressure and cardiac output and a slight increase in heart rate within 5 hours after intragastric administration of 0.7 g/kg methyl salicylate to dogs. Methyl salicylate-induced changes in various metabolic parameters were thought to be responsible for resulting myocardial failure and skeletal (hind limb) muscle necrosis; these included increased levels of creatine phosphokinase (CPK) in coronary effluent and skeletal muscle bed, a marked net efflux of both K^+ and lactate from the muscle bed, and a steady rise in oxygen consumption. It was concluded that hyperkalemia was produced by a methyl salicylate-induced uncoupling of oxidative phosphorylation, which caused a reduction in the level of high energy phosphate necessary to maintain the normal muscle cell membrane potential, thus altering the transport of K^+. The exact mechanism and site of uncoupling was not determined (Ojiambo, 1971b,d). Ojiambo (1971a) also suggested that increased arterial levels of catecholamines (epinephrine and norepinephrine) in dogs intoxicated by methyl salicylate may have been a factor in the skeletal and cardiac cell damage.

In a subchronic feeding study, Webb and Hansen (1963) observed growth retardation but no gross or microscopic abnormalities in 20 rats fed 10,000 ppm methyl salicylate in the diet (1%) for 17 weeks. No effects were observed in rats fed 1,000 ppm (0.1%). Harrison et al. (1963) reported an increase in cancellous (i.e., spongy) bone in the femurs and tibias of rats fed 20,000 or 11,250 ppm methyl salicylate in the diet for 10 weeks, while no effects were observed with levels of 2,000 3,550, 6,330 or 9,000 ppm.

Weight loss and death within a month were observed in pairs of dogs given daily capsules of 500, 800 or 1200 mg/kg methyl salicylate 6 days/week. At the two highest dosage levels, moderate to marked amounts of fatty metamorphosis were noted in the liver. No adverse effects were noted in 8 dogs given daily capsules of 50, 100 or 250 mg/kg, 6 days/week for up to 59 days (Webb and Hansen, 1963).

Anorexia, weight loss, depression and death in 6-28 days occurred in 3 rabbits after application to the clipped back with 4 ml/kg/day methyl salicylate, 5 days/week. In one case, microscopic examination of tissue showed several distinct lesions indicative of kidney damage. Applications of 2, 1 or 0.5 ml/kg/day, 5 days/week for up to 96 days resulted in a slight to very slight dermatitis and an increased incidence of spontaneous nephritis and mild hepatitis. Two of 3 rabbits treated with 2 ml/kg/day showed a slight sloughing of the epidermal scales (Webb and Hansen, 1963).

Gage (1970) reported no signs of toxicity or organ abnormalities in rats after twenty 7-hour exposures to saturated methyl salicylate vapor (120 ppm, 700 mg/m^3).

- Chronic Toxicity

In a 2-year feeding study, growth retardation, rough coats and death within 49 weeks were observed in 50 rats fed 20,000 ppm methyl salicylate in the diet (2%). Pneumonia was the only obvious gross lesion, occurring in 29/50 (58%) of the treated animals; this condition was more acute and resulted in more lung abscesses in the treated rats compared to control rats. Although no other gross lesions were apparent, it must be noted that all the treated rats died before the usual age at which spontaneous lesions develop.

Hematological analyses were negative, while microscopic examination revealed an excess of cancellous tissue in the bone. Addition of 10,000 ppm methyl salicylate to the diet (1%) for 2 years caused growth retardation and rough coats. Both 10,000 ppm (1%) and 5000 ppm (0.5%) in the diet caused a slight excess in cancellous tissue in the bone. No gross or microscopic effects were noted with addition of 1,000 ppm (0.1%) (Webb and Hansen, 1963).

In the same study, weight loss and growth retardation were noted in 7 dogs given daily capsules of methyl salicylate (150 or 350 mg/kg/day), 6 days/week for 2 years. Gross examination revealed enlarged livers, and microscopic examination showed enlarged hepatic cells, but no excess fatty metamorphosis. No effects were noted in 4 dogs dosed with 50 mg/kg/day for 2 years (Webb and Hansen, 1963).

- Skin Irritation/Sensitization

A number of studies have reported various dermal effects of methyl salicylate applied to rabbit, rat or guinea pig skin. Moreno (1973) found methyl salicylate to be a moderate irritant to intact or abraded rabbit skin when applied full strength for 24 hours under occlusion. Similarly, Yankell (1972) noted mild to moderate irritation following application of 1,3 or 6% methyl salicylate in several different vehicles to intact rabbit skin (shaved and depilated) for 24-72 hours with occlusion (Saran® wrap). Results were as follows:

	Irritation Index*		
	methyl salicylate concentration		
Vehicle	1%	3%	6%
H_2O suspension	-	0.83 (mild)	1.83 (mod.)
PEG 400	0.33 (mild)	0.50 (mild)	0.50 (mild)
70% ethanol	1.17 (mild)	4.17 (mod.)	4.00 (mod.)
70% ethanol with emollients	2.17 (mod.)	3.00 (mod.)	3.00 (mod.)

* According to the Draize Method

Slight erythema and edema were noted after 24 hours with 1% methyl salicylate in 70% ethanol, while necrosis was observed with the 3% and 6% formulations. Necrosis and intradermal and subcutaneous hemorrhage were produced with all three concentrations of methyl salicylate in 70% ethanol with emollients. Polyethylene glycol (PEG) reportedly inhibits the penetration of methyl salicylate into the skin and/or decreases its release from solution. Similarly, the addition of emollients has been reported to cause release of only a part of the total amount of methyl salicylate from an ethanol solution.

In a skin sensitization test, methyl salicylate caused no significant allergic reactions in guinea pigs. Twenty animals received one intracutaneous injection of 0.1% methyl salicylate in Freund's adjuvant and saline every other day for 3 weeks for a total of 10 applications. Fourteen days after the last injection, a challenge dose of 1 ml of 0.1% methyl salicylate was administered by intradermal injection. Positive allergic

reactions were noted in 2/20 (10%) treated animals compared to 0/20 in controls ($P>0.01$). A second challenge dose of methyl salicylate, administered 10 days later by the epidermal route, consisted of a maximal subirritant concentration (10%) applied in soft white petrolatum under occlusive dressings for 24 hours. No allergic reactions were observed in any of the 20 treated animals (Maurer et al., 1980).

- Hematological Effects

Salicylates have been known to interfere with the synthesis of vitamin K_1-dependent clotting factors VII, IX and X, and also to prolong prothrombin time in vitamin K_1-deficient rats and rabbits. Park and Leck (1981) observed significant decreases in prothrombin complex activity (PCA) and in levels of vitamin K_1-dependent clotting factors II, VII and X (but not V) in rabbits following intramuscular injection of 1 g/kg methyl salicylate (in a split dose). Despite this high dose, recovery of normal plasma PCA occurred after about 30 hours, or within 2 hours if 2 mg/kg vitamin K_1 was administered intravenously. The reappearance of PCA was directly related to plasma salicylate levels, with total suppression of the synthesis of PCA (indicating complete inhibition of clotting factor synthesis) occurring at a minimum salicylate level of 355 ± 12 µg/ml. The data indicated that methyl salicylate elicited its effect on the vitamin K_1-epoxide cycle at the epoxide reductase step, thus preventing regeneration of vitamin K_1 and causing a reduction in clotting factor synthesis. Although salicylates are not known to produce hypothrombinemia at normal therapeutic doses, the authors suggested that such an effect could occur with an overdose or with a normal dose taken simultaneously with another drug which affected vitamin K_1 concentrations in the liver.

- Reproductive Effects/Teratogenicity

A number of studies have reported increased incidences of teratogenic effects in rats and hamsters following induction of methyl salicylate poisoning in pregnant dams during the early stages of embryonic development. To our knowledge, however, congenital malformations attributable to methyl salicylate or salicylate intake by the mother have not been recorded in man.

Single subcutaneous injection of 0.1 ml methyl salicylate to pregnant rats on day 10 or 11 of gestation resulted in incidences of fetal resorption of 27.3 and 32.7%, respectively, and fetal abnormalities in 31.4 and 18.2%, respectively, of the live births. Most abnormalities involved the cardiovascular, urogenital and/or skeletal systems. Retarded fetal growth, abnormalities of the branchial arch arterial derivatives, cleft lip, cleft palate and hydroureter were commonly seen; "club-foot" and phocomelia of the hind-limbs were frequently seen after injection on day 11. Hydronephrosis, ectopic kidneys, and exencephaly were occasionally observed. Greater frequencies of resorption and fetal abnormalities were apparent when administration of methyl salicylate was combined with hypoxia for 6 hours (25,000 feet altitude equivalent). It was suggested that hypoxia aggravated the increased utilization of oxygen by the tissues which was induced by the methyl salicylate (Bertone and Monie, 1965).

Warkany and Takacs (1968) observed even higher incidences of abnormalities in rats following single subcutaneous injections of 0.1-0.5 ml

methyl salicylate to 116 pregnant dams on days 9, 10 or 11 of gestation. Results of treatment included 26 maternal deaths (22.4%), 47 resorptions (40.5%) and 120 fetal abnormalities among 298 live births (40.3%). No fetal abnormalities were noted in 484 live births from 59 untreated controls. Congenital malformations included 4 cases of exencephaly, 4 cases of hydrocephalus and 9 cases of harelip, oblique facial clefts and/or cleft palate. Some anomalies of the vertebrae and ribs were noted, while in only 2 cases were the bones of the extremities grossly deformed. Of special note in this study was the occurrence of 12 cases of craniorachischisis, a congenital fissure of the skull and spinal column; 5 of these 12 also had gastroschisis with protrusion of the stomach, liver and intestine. This condition was thought to be comparable to early stages of craniorachischisis in humans (Warkany and Takacs, 1968).

In an extension of the above study, using the same methods, Takacs and Warkany (1968) observed induction of cardiovascular malformations in 30/159 (18.9%) fetuses removed on day 21 of gestation from methyl salicylate-treated dams. The most common abnormality was transposition of the aorta to the right, with displacement ranging in degree from "overriding aorta" to complete transposition. In addition, there were 2 cases of isolated ventricular septal defects and two dextrocardias.

Similarly, Woo and Hoar (1971, 1972) found that intraperitoneal injection of 0.05 or 0.1 ml methyl salicylate to pregnant rats on days 10 or 11 of gestation caused a retardation in renal development, particularly growth of renal papilla. During the normal pattern of renal development in the rat fetus the renal papilla increase slowly and steadily in length, while the renal parenchyma increases rapidly and almost exponentially in weight, resulting in an abnormally large renal pelvis and "apparent hydronephrosis" late in gestation. This apparent abnormality decreases by steady lengthening of the renal papilla with advancing fetal and postnatal age, and generally disappears shortly after birth. Treatment of pregnant females with methyl salicylate appeared to inhibit the lengthening of the renal papilla and caused reduced kidney weights through some effect on renal growth. This resulted in an increased number of kidneys with an apparently enlarged renal pelvis. In addition, a higher frequency of fetuses from treated dams had kidneys with no papilla at all. Some recovery from methyl salicylate-induced effects was apparent, with kidney weights and renal papillary lengths nearly normal by postnatal day 6. However, gross dilation of the renal pelvis, reduction of renal parenchyma, and papilla of narrower circumference (although of normal length) were noted in 11/138 (8%) of the treated fetuses at weaning. This persistent condition, suggestive of hydronephrosis or hypoplasia, was not noted in control fetuses.

Monie (1970) noted occurrences of hydronephrosis and hydroureter in fetuses from similarly treated rats. In some cases these abnormalities were associated with an obstruction or structural aberration in the urinary tract, while in some, the urinary tract was unobstructed and terminated normally. In the latter cases, the dilatation may have been a result of neuromuscular imbalance. In all cases, there was a reduction in the number of glomeruli and retarded development of the renal tubules; usually the collecting tubules were dilated and shortened.

A variety of reproductive effects were noted when groups of 20 rats were fed 500, 1,500, 3,000 or 5,000 ppm methyl salicylate in the diet for 3 generations. Although no significant decrease was observed in the fertility index at any dosage level or generation, notable decreases were observed in average litter size, average number of liveborn progeny, viability index, the number of progeny surviving 4 days and the number surviving to weaning at dose levels of 3,000 and 5,000 ppm methyl salicylate. These decreases were most significant in the second generation. Combined results from all 3 generations indicated an apparent dose-related response, starting at 1500 ppm, in the average litter size, number of liveborn progeny and the number of day 4 survivors. No grossly visible abnormalities were observed in external examinations of newborns or weanlings from any generation; autopsies and histological examinations of third generation weanlings revealed no abnormalities or evidence of toxicity (Collins et al., 1971).

Both topical and oral administration of methyl salicylate to pregnant hamsters on day 7 of gestation reportedly resulted in failure of neural tube closure in nearly 75% of the embryos recovered at day 9. However, in order for topical administration to result in blood salicylate levels equal to those caused by oral administration, a topical dose more than 8 times larger than the oral dose was necessary (~14g/kg compared to 1.75 g/kg methyl salicylate). Also, the level of salicylates in the blood increased much more gradually following topical application compared to oral administration, with maximum levels occurring at 5-6 hours and 2 hours, respectively. The authors suggested that although absorption of methyl salicylate through the hamster skin could induce teratogenic effects similar to those obtained after oral treatment, the response required very large topical doses (Overman, 1979; Overman and White, 1978).

White (1978) reported that variations in the teratogenic response in hamsters to methyl salicylate was affected by differences in fetal age which apparently correspond to different intrauterine positions. When pregnant hamsters were given oral doses of 175-225 mg methyl salicylate per 100 g body weight at specific times during the period of gestation from day 7 hour 9 to day 7 hour 22, the frequency of cranium bifida in embryos at day 9 ranged from 16-73%, compared to 11% in controls. The critical importance of timing was indicated by the fact that treatment at hour 21 resulted in a significant frequency of defects, while treatment just one hour later, at hour 22, induced a frequency of defects not statistically different from the control value.

Szabo et al. (1971) reported that methyl salicylate was embryotoxic and teratogenic in both mice and rabbits when administered during pregnancy (doses, route and time of administration not stated). Malformations included cleft palate, exencephaly, hydrocephalus, amphalocele, open eyelid and spina bifida.

It should be noted that the doses of methyl salicylate which induced teratogenic effects in these studies were close to dose levels which are lethal to the embryo and toxic to the dam, thereby decreasing the expected yield of offspring. Also these doses were, on a weight basis, far greater than therapeutic human doses. Takacs and Warkany (1968) estimated that an

equivalent dose in humans to that inducing a teratogenic response in rats would require intake of approximately 30 g of salicylates ingested by a 60 kg female during early gestation.

- Carcinogenicity

No increase in the incidence of lung tumors was noted in strain A mice given 24 intraperitoneal injections of a maximum tolerated dose of methyl salicylate or 20% of this dose over an 8 week period; the actual doses administered were not stated (Stoner et al., 1973).

Metabolic Characteristics

Human Data

Methyl salicylate is rapidly absorbed through intact human skin or by ingestion. It is hydrolyzed in the stomach to methyl alcohol, and salicylic acid which is converted to sodium salicylate in the intestine and absorbed. Although largely hydrolyzed, it is also absorbed, at least in part, as the intact ester. Methyl alcohol is seldom produced in sufficient quantities to be a factor in intoxication; approximately 75% of the methyl salicylate is available as salicylate (Gosselin et al., 1976; Adams et al., 1957).

Salicylate is rapidly distributed throughout all body fluids and can be detected in synovial, spinal and peritoneal fluid, saliva, bile and milk. The intact ester is also hydrolyzed in the plasma and tissues to salicylic acid and its metabolites. Approximately 70-80% of the salicylate in human plasma is bound to non-diffusible components, presumably plasma protein. Salicylates are excreted in the urine in the form of salicylates or their metabolites. Small amounts of unhydrolyzed ester may also be excreted, giving the urine a slight odor of wintergreen (Adams et al., 1957).

Maruta and coworkers (1977) observed peak serum concentrations of free salicylic acid (4 µg/ml) and total salicylates (12.5 µg/ml) 8 and 12 hours, respectively, after initiation of a single 12-hour application to the backs of human volunteers of 10 plasters, each containing 350 mg methyl salicylate and covered with plastic film. Levels of salicylates were negligible at 24 and 48 hours after application. Urinary excretion of total salicylates reached a plateau of approximately 37 percent 24 hours after application, with little to no free or total salicylates measured in the urine by 36-48 hours. Following repeated 12-hour applications, each 12 hours apart, for 6 days, only trace to no free salicylic acid or total salicylates were detected 12 hours after removal of the 2nd, 4th or 6th plaster and no salicylates were detected 36 hours after the last (6th) application. Thus, salicylates did not appear to accumulate in the human body at this dose level, even with repeated application.

Several studies have indicated that hydrolysis of methyl salicylate in humans is slower and of lower magnitude than that seen in dogs or rats. An appreciable amount of unhydrolyzed methyl salicylate was measured in plasma 15 minutes (39%) and 90 minutes (21%) after ingestion of 0.42 ml methyl salicylate in ginger ale. Total plasma salicylate concentrations were significantly less than those obtained after similar administration of acetylsalicylic acid. In tests with dogs, negligible amounts of methyl

salicylate were measured in the total plasma salicylates within 60 minutes after oral administration of a much higher dose than that administered to humans (equivalent to ~300-500 mg/kg salicylic acid compared to ~7 mg/kg). Other reports have also indicated that lethal concentrations of total circulating plasma salicylates in man were 2-3 times higher than those in dogs at the time of death. It has been suggested that large doses of methyl salicylate administered to humans could overwhelm an apparently inadequate detoxification mechanism, resulting in even less hydrolysis, greater uptake of the highly lipid-soluble undissociated ester by such tissues as the brain, and a consequent increase in toxicity. In 3 cases of accidental ingestion of ~30-90 ml of methyl salicylate, about 21% of the dose was still circulating in the plasma at the time of myocardial failure (Ojiambo, 1971c; Davison et al., 1961).

Animal Studies

Absorption of topically applied methyl salicylate was shown to be quite rapid in mice and rabbits. High levels of radioactivity were measured in the skin of hairless mice at the exposure site within 1 hour after percutaneous application of a plaster containing 127 mg/kg [^{14}C]-labelled methyl salicylate for 1, 2, 4, 8, 12, 24 or 48 hours. Levels of activity peaked at 4 hours, then gradually decreased until virtually no activity was measured at 48 hours. Only slight radioactivity was detected in the skin adjacent to the application site at 2 and 4 hours. Serum levels of radioactivity peaked (equivalent to 15 µg/ml salicylates) 2 hours after application, then decreased gradually. Cumulative urinary excretion of radioactivity was 33.5 and 39.3% of the dose in mice treated for 24 and 48 hours, respectively. It appeared that the methyl salicylate was absorbed rapidly from the plaster and was localized at a high concentration in the skin at the application site (Maruta et al., 1977).

Kitagawa and coworkers (1979b) noted an even higher rate of absorption of radiolabeled methyl salicylate when applied to rabbit skin. Radioactivity was detected in the blood 15 minutes after application and peaked at 2 hours after administration. Distribution of methyl salicylate was widespread, with radioactivity observed in nearly all organs and tissues. Excretion was also rapid, with total radioactivity (32.88% of the dose) eliminated in the urine at 94 hours; no radioactivity was found in the feces.

Kida (1978) found that percutaneous absorption of methyl salicylate from the back of rabbits, pigs and humans could be increased by raising the temperature of the methyl salicylate-containing poultice.

Several studies have indicated that more extensive hydrolysis of methyl salicylate occurs in the intestine after oral administration compared to other routes of administration. Williams (1959) reported that only 0.2-0.5% of an oral dose of 0.2 g/kg appeared unchanged in the urine of dogs, while 14% of the dose appeared unchanged in the urine after intramuscular injection. Similarly, Davison et al. (1961) noted from plasma analyses that hydrolysis was about 95% complete at 1 and 4 hours in dogs given capsules (orally) of 300 mg/kg methyl salicylate. Ojiambo (1971a) observed an initial 1 hour delay in the absorption of methyl salicylate, followed by a steady linear rise in plasma salicylate levels up to 3 or 4 hours after intragastric administration of 700 mg/kg methyl salicylate to dogs. No

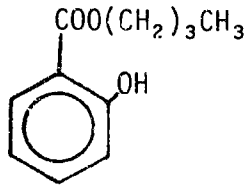
further significant increase in blood salicylate levels was observed after 3 hours in dogs surviving the treatment or after 4 hours in dogs dying within the study period. The data indicated a higher rate of absorption and/or a slower rate of elimination in the dogs that died within 5 hours of treatment (3 of which had received an additional 100 mg/kg methyl salicylate 2 hours after the first dose). The initial delay in appearance of salicylate in the blood was attributed to a delay in passage of methyl salicylate into the small intestine from the stomach, possibly due to spasm of the pylorus caused by gastric irritation. Once absorption was initiated, hydrolytic and detoxification mechanisms converted the methyl salicylate to its metabolites. Ojiambo (1971c) also indicated that the level of total plasma salicylates which resulted in death of female dogs was lower than that of male dogs.

In a similar study, plasma and brain tissue analyses from rats demonstrated negligible amounts of methyl salicylate 20 and 60 minutes after administration by oral catheter of a dose equivalent to 500 mg/kg salicylic acid. Thus, hydrolysis of this near lethal dose was almost complete in as little as 20 minutes (Davison et al., 1961).

Monitoring and Detection

Methyl salicylate would be rapidly converted by esterases to salicylic acid (o-hydroxybenzoic acid). The metabolites of salicylic acid include salicyluric acid (glycine conjugate), the acyl and phenolic glucuronides, gentisic acid and gentisuric acid. Salicyluric acid would be the major metabolite (~80%) in urine. Salicylic and salicyluric acids may be readily analyzed in either plasma or urine samples by high performance liquid chromatography (Sadee and Beelen, 1980). The assay is sensitive to 0.5 µg/ml for both compounds. A gas chromatographic procedure is reported for the analysis of methyl salicylate in either plasma or urine; however, the method is based on 20 µg of compound/ml plasma (Pentz and Schutt, 1978). This concentration is much higher than can be expected under simulant training conditions. Acetylsalicylic acid (aspirin) would give the same metabolic products as the salicylate esters. Therefore, unless the salicylate esters can be detected in plasma, urine or saliva, military personnel would have to forego use of aspirin as a pain reliever prior to any military exercise.

Possible qualitative tests for the detection of salicylate esters on either clothing or equipment include ultraviolet light and 5% aqueous ferric chloride spray (greenish-blue color) (Walash and Hassan, 1978).

Simulant:	Butyl Salicylate
Formula:	
CAS Reg. No.:	2052-14-4
Molecular Weight:	194.25
Chemical State (20°C):	colorless liquid
Liquid Density (g/cc):	1.13 (Lyman et al., 1982)
Vapor Density (compared to air):	6.74 (Lyman et al., 1982)
Freezing/Melting Point (°C):	
Boiling Point (°C):	268.3°
Flash Point (°C):	
Vapor Pressure (mm Hg at 20°C):	0.0043
Volatility (mg/m^3):	46 (Lyman et al., 1982)
Viscosity (cp at 20°C):	20.3 (Lyman et al., 1982)
Odor:	
Action on Metals or Other Materials:	
Reference Source(s):	RTECS (1980); Hoy (1970); Lyman et al. (1982)

BUTYL SALICYLATE

Potential Health Effects

Butyl salicylate is a colorless liquid formed by direct esterification of n-butanol with salicylic acid under azeotropic conditions; it does not occur in nature. Butyl salicylate is used as a fragrance in commercial products and as a flavoring substance in food. It has been given GRAS status by the Flavor and Extract Manufacturers' Association (Food Chemical News Guide, 1982). The Council of Europe (1974) noted that 0.5 ppm butyl salicylate may be added to foodstuffs with no hazard to public health. Maximum reported use levels as a fragrance include 0.1% in soap, 0.01% in detergents, 0.03% in creams and lotions and 0.4% in perfumes; typical use concentrations are about an order of magnitude less than the maximum levels (Opdyke, 1978c).

Human Data

No irritation to human skin was produced following application of 2% butyl salicylate in petrolatum in a 48-hour closed-patch test (Kligman, 1975). In a maximization test with 25 volunteers, this same concentration of butyl salicylate caused no sensitization reactions (Kligman, 1975).

No additional information on the effects of butyl salicylate exposure in humans was found.

Animal Studies

The acute oral LD_{50} of butyl salicylate in rats was reported as 1.7 g/kg (1.26-2.29 g/kg) and the acute dermal LD_{50} in rabbits was reported as >5 g/kg (Levenstein, 1975).

Undiluted butyl salicylate was not irritating to rabbits when applied to either intact or abraded skin for 24 hours under occlusion (Levenstein, 1975).

Butyl salicylate has been shown to possess bacteriostatic and antimicrobial activities against a variety of bacteria, yeast and fungi (Oka, 1962; Yamamoto et al., 1967; Zsolnai 1960).

No additional toxicity data were found for this compound.

Metabolic Characteristics

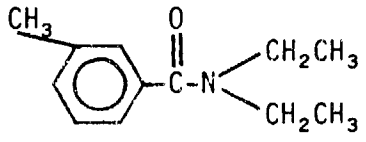
No data were found on the metabolic fate of butyl salicylate in animals or humans. Based on available information for methyl salicylate, however, one would expect butyl salicylate to be hydrolyzed to butyl alcohol and salicylic acid. The salicylic acid would most likely be excreted as the glucuronide.

Monitoring and Detection

Butyl salicylate would be rapidly converted by esterases to salicylic acid (o-hydroxybenzoic acid). The metabolites of salicylic acid include

salicyluric acid (glycine conjugate), the acyl and phenolic glucuronides, gentisic acid and gentisuric acid. Salicyluric acid would be the major metabolite (~80%) in urine. Salicylic and salicyluric acids may be readily analyzed in either plasma or urine samples by high performance liquid chromatography (Sadee and Beelen, 1980). The assay is sensitive to 0.5 µg/ml for both compounds. A gas chromatographic procedure is reported for the analysis of methyl salicylate in either plasma or urine; however, the method is based on 20 µg of compound/ml plasma (Pentz and Schutt, 1978). This concentration is much higher than can be expected under simulant training conditions. Acetylsalicylic acid (aspirin) would give the same metabolic products as the salicylate esters. Therefore, unless the salicylate esters can be detected in plasma, urine or saliva, military personnel would have to forego use of aspirin as a pain reliever prior to any military exercise.

Possible qualitative tests for the detection of salicylate esters on either clothing or equipment include ultraviolet light and 5% aqueous ferric chloride spray (greenish-blue color) (Walash and Hassan, 1978).

Simulant:	N,N-Diethyl-m-toluamide
Formula:	
CAS Reg. No.:	134-62-3
Molecular Weight:	191.26
Chemical State (20°C):	colorless to amber liquid
Liquid Density (g/cc):	d_4^{20} 0.996
Vapor Density (compared to air):	6.63 (Lyman et al., 1982)
Freezing/Melting Point (°C):	
Boiling Point (°C):	288-292°
Flash Point (°C):	
Vapor Pressure (mm Hg at 20°C):	0.0056
Volatility (mg/m^3):	59 (Lyman et al., 1982)
Viscosity (cp at 20°C):	16.6 (Lyman et al., 1982)
Odor:	nearly odorless
Action on Metals or Other Materials:	
Reference Source(s):	RTECS (1980); Sax (1979); Stecher (1968); Lyman et al. (1982); Ambrose (1959)

DIETHYL TOLUAMIDE

Potential Health Effects

Diethyl-m-toluamide (m-Det) is a colorless or faintly yellow liquid with a faint pleasant odor. Solutions of 50 to 75% m-Det are widely employed as an insect repellent (e.g., Off®) which is applied directly to skin or clothing.

Human Data

Available human studies on exposure to m-Det in the published literature consist of short-term dermal contact or accidental ingestion by children.

A single application of neat m-Det to the forearm of human volunteers produced no irritation (Phillips et al., 1972). Concentrations of 50% and 100% m-Det (in ethanol) were classified as non-irritants in a 21-day continuous open patch test applied to the backs of four test subjects (0.02 ml daily). Skin irritation was noted, however, in a similar 21-day continuous occlusive patch test. Cumulative irritation scores were 9, 18.5, 61, 50.5, 48 and 21 of a possible 84 points for concentrations of 1, 10, 20, 40, 60 and 80% m-Det, respectively (Phillips et al., 1972).

Repeated daily application of a 50% solution of m-Det (in isopropanol) to the face and arms of human volunteers over a five day period produced no irritation, but some desquamation and facial dryness was noted by the third day (Ambrose, 1959). Similar symptoms were observed in one individual who treated his face with the same preparation for three consecutive days each week for a total of six weeks (Ambrose, 1959).

Two reports of human hypersensitivity to m-Det have been mentioned in the literature (Maibach and Johnson, 1975; Lamberg and Mulrennan, 1969). Maibach and Johnson (1975) described an individual who developed contact urticaria of the immediate hypersensitivity type within 20 minutes of topical application of m-Det. The contact urticaria was localized to the site of application. Studies with the patient's serum indicated the response could be passively transferred, suggesting a possible immunologic response mechanism. Occlusive patch tests for delayed hypersensitivity at two and four days were negative.

Lamberg and Mulrennan (1969) implicated m-Det as the agent responsible for bulbous eruptions noted in the antecubital fossae of U.S. military personnel in South Vietnam. These investigators applied 75% m-Det in a 48-hour patch test to the antecubital fossae of 77 volunteers, 37 of which (48%) exhibited severe contact dermatitis. Similar application to the upper inner part of the arm produced no reaction in 62 test subjects.

Four reports have suggested a possible link between seven cases of toxic encephalopathy, two of which were fatal, and exposure to m-Det. Four cases are well documented in the literature: all occurred in children, all female and all under six years of age (Gryboski et al., 1961; Zadikoff, 1979; Heick et al., 1980). Reports on the three remaining cases were available only in abstract form, and indicated that three individuals developed encephalopathy secondary to ingestion of m-Det. All recovered. No additional details were

given in the abstract (Tenenbein, 1981). The affected children are all believed to be deficient in ornithine carbamoyltransferase (OCT), a liver enzyme which is intimately involved in urea synthesis. OCT deficiency, a sex-linked condition, is fatal to males in neonatal life. Females can survive but display an aversion to protein and a liability to encephalopathic states and other syndromes of hepatic disorders.

Exposures to m-Det in the four encephalopathic cases described in the literature ranged from ingestion of an unknown but probably small amount of insect repellent containing 10% m-Det by an 18-month-old girl (Zadikoff, 1979), to a single extensive spraying of a child with 15% m-Det (Heick et al., 1980) or repeated nightly spraying for almost three months with 10% m-Det prior to manifestations of illness (Zadikoff, 1979). Toxic manifestations included disorientation, ataxia, slurred speech, extreme irritability, bizarre limb movements and periods of shaking and crying out.

These reports of toxic encephalopathy suggest caution in the use of m-Det by people who are known or suspected to be deficient in OCT.

Animal Studies

- Acute and Subchronic Effects

Acute oral LD_{50} values for technical grade m-Det range from 1585 mg/kg for the rabbit (Haight et al., 1980) to 2000-3290 mg/kg for the rat (Kellner et al., 1981; Haight et al., 1980). An apparent difference in response between the sexes is noted in rats, with females somewhat more sensitive than male rats (i.e., an LD_{50} of 2420 mg/kg for females compared to 3290 mg/kg for male rats) (Haight et al., 1980).

LD_{50} values for 24-hour occluded dermal exposures were 4903 mg/kg in female rats and 4154 mg/kg in males (Macko and Weeks, 1980). The dermal LD_{50} value for rabbits was 4340 mg/kg (Macko and Weeks, 1980).

Inhalation LC_{50} values of 5860-6000 mg/m^3 were reported for rats by Sherman (1979).

Manifestations of acute toxicity in rats include lacrimation, chromodacryorrhea, depression, prostration, epileptoid tremors and asphyxial convulsions. Respiratory failure usually preceded cardiac failure. Evidence of hyperemia of lungs, intestinal irritation and kidney congestion was seen at necropsy (Ambrose, 1959).

No cumulative toxic effects were observed in rabbits following five repeated daily intravenous injections of 25 mg/kg m-Det. Rapid injections caused temporary miosis and collapse, while slow injections elicited no such effects. Single intravenous doses greater than 50 mg/kg were rapidly fatal (Ambrose, 1959).

Ambrose (1959) also observed no significant toxic effects in rats exposed 8 hours per day, 5 days per week for 7 weeks to air saturated with m-Det (~1 ml m-Det/14,000 L air/40 hr exposure period). Increased activity and scratching of nares were noted during the first few minutes of exposure and slight hyperemia of the ears, feet and tails and slight bloody discharge

around the nares after 2 hours. No deaths, no effects on growth and no gross pathological effects were observed. Minor microscopic changes in trachea and lungs were seen, but no other histological abnormalities were evident. A similar response was recorded for rats exposed to an aerosol of 85% m-Det (mean particle size ~2μ) for 2 to 6 hours (Ambrose, 1959).

Results of a battery of behavioral tests given to rats following a single four hour exposure to an aerosol of m-Det at concentrations of 2300, 2900 or 4100 mg/m^3 permitted distinctions (at 0.01 level) of performance in a dose-related manner (Sherman, 1979).

Subchronic oral administration of m-Det (0.1 or 0.3 ml/kg/day) to dogs for 13 weeks produced mild CNS stimulation (tremors and hyperactivity) and occasional emesis but no other signs of toxicity. Histopathological findings were reportedly within normal ranges (Keplinger et al., 1961).

Histopathological changes in male New Zealand white rabbits given 15 daily oral doses of 132, 264 or 528 mg m-Det/kg body weight indicated rare to minimal fatty changes in hepatocytes in a suggestive dose-related pattern. Serum clinical chemistries indicated a significant decrease in calcium and an increase in cholesterol and triglyceride levels after 7 days at the 528 mg/kg dose. Rabbits in this treatment group also showed a progressive decrease in body weight which became statistically significant after 7 days. An initial slight decrease in body weight was also noted in the 264 and 132 mg/kg groups as well as controls but recovered after 6 days. Relative kidney weights in the high dose group and lung weight in the 264 mg/kg group were increased over controls but no histopathological changes were seen (Haight et al., 1980).

Ambrose (1959) observed no significant effect on growth, mortality, food consumption, organ weights, hemoglobin or organ histology in rats fed 0.01, 0.05, 0.1, 0.5 or 1.0% m-Det in the diet (~100, 500, 1000, 5000 and 10,000 ppm) for 200 days. A 10% inhibition in growth was noted at the highest dose level beginning at about day 70 but was not associated with food consumption or any gross or microscopic pathological findings. Blood cholinesterase values (red cells and plasma) and hemoglobin were normal. There was some suggestion of testes hypertrophy at 0.1, 0.5 and 1.0% levels and liver and kidney weights of females in the 1.0% treatment group were also elevated.

Ninety day dermal studies conducted with dogs (0.3 ml/kg/day) and rabbits (0.5-3 ml/kg/day) produced no systemic toxicity except for moderate to severe skin irritation at doses greater than 1 ml/kg. Histopathological examination indicated slight damage to rabbit kidneys, reported to be typical of that associated with burns of the skin (Keplinger et al., 1961).

- Skin Irritation/Sensitization Studies

Single 24 hour applications of 0.5 ml technical grade m-Det to intact and abraded skin of New Zealand white rabbits produced slight to well defined erythema of intact and abraded skin areas at 24 and 72 hours and slight edema in one animal at 24 hours. Irritation scores ranged from zero to two on a scale of eight, resulting in a classification of a mild irritant (Macko and

Weeks, 1980). Similar findings were reported by Phillips et al. (1972). Macko and Weeks (1980) also indicated that m-Det was not a photochemical irritant.

A 24 hour occlusive patch test (2 or 4 ml m-Det/kg body weight) with rabbits resulted in mild to moderate erythema which subsided 24 hours after removal of the patch. Complete recovery was seen within 5 days (Ambrose, 1959).

Palmer (1969) observed no ill effects in horses following single topical applications of aerosol sprays containing up to 75% m-Det. Signs of dermatosis were seen; however, in horses given daily mist application with concentrations of 15% m-Det or greater for 60 days. The most severe dermatosis occurred with concentrations of 50 or 75% m-Det. The outer layers of flank skin cracked and appeared ulcerated with accompanying inflammation.

Repeated daily application of 50% m-Det in either cottonseed oil or isopropanol (~1 g m-Det/kg body weight) to intact skin of rabbits, 5 days per week for 13 weeks was characterized by slight to moderate erythema, desquamation and dryness of skin. By the third or fourth week of treatment, the integument of the skin became leathery, hard, and dry and fissures developed. Desquamation persisted throughout treatment. No lethalities occurred and growth and behavior were normal. The skin had returned to normal 3 weeks post-treatment although some scarring remained (Ambrose, 1959). Similar effects, but to a lesser degree, were seen in rabbits treated with 0.25 or 0.5 ml m-Det/kg for 20 days (Ambrose, 1959).

There are no indications that m-Det is a skin sensitizer in guinea pigs. Intradermal injections of guinea pigs with a 0.1% suspension of m-Det (in saline:propylene glycol mixture) and subsequent challenge two weeks after the last injection did not produce a sensitization reaction (Macko and Weeks, 1980). Ambrose (1959) also reported a negative response in guinea pigs given ten daily dermal applications of 10% m-Det (in isopropanol), then challenged 15 days following the final treatment. A third report by Zakamardin (1969) also notes the lack of a sensitization reaction in guinea pigs treated with 80% m-Det.

- Ocular Effects

Diethyl-m-toluamide is an ocular irritant. Instillation of 0.1 ml technical m-Det into the eyes of New Zealand white rabbits produced corneal damage, iritis and conjunctivitis at 24, 48 and 72 hours. Corneal opacity and iritis were reversible within 7 days but conjunctivitis was still present in one of six test animals at 7 days. Washing the treated eye for 60 seconds with water 20 seconds after instillation of m-Det decreased the irritation; very slight corneal damage and iritis were noted at 24 hours but not at 72 hours. Conjunctivitis was present in all six test rabbits at 24 and 48 hours, only two animals at 72 hours and absent at 7 days (Macko and Weeks, 1980).

Moderate to marked edema, lacrimation, conjunctivitis, pus and varying degrees of corneal injury were observed in the eyes of rabbits treated with

one drop of undiluted m-Det or three drops of either a 30% or 40% solution of m-Det in cottonseed oil. Effects were still present after 48 hours (Ambrose, 1959).

Kellner and coworkers (1981) tested the ocular irritancy of two m-Det formulations in New Zealand white rabbits. The two formulations consisted of a 75% concentration of m-Det in ethanol and a suspension of 50% m-Det in 25% Dow Corning 200 Fluid® (a dimethyl siloxane polymer) and 25% isopropyl alcohol. A 0.1 ml dose of either formulation was instilled into eyes of 9 rabbits; 3 rabbits in each treatment group received a 60 second eye wash with water 30 seconds after instillation, the remaining rabbits did not. Both formulations were classified as ocular irritants. The 50% m-Det suspension produced more irritation than the 75% ethanolic solution, particularly with respect to corneal opacity. The ocular toxicity produced by both formulations persisted approximately 13 days. Flushing the treated eyes, however, had a beneficial effect on both test groups.

- Carcinogenicity

No data were found dealing with the carcinogenicity of m-Det.

- Mutagenicity

There is no evidence to suggest any mutagenic activity for m-Det. Swentzel (1977) reported negative results in a dominant lethal assay with ICR/Ha Swiss mice given a single gavage dose of m-Det (600 mg/kg) in corn oil. Males were mated with three virgin females weekly for eight weeks. Even though no dominant lethal response was induced, a slight decrease was noted in the total number of implants per pregnancy compared to controls. The 8-week mean (11.4) for implants per pregnant female from the m-Det group was only slightly below the historical mean weekly total implants per pregnancy (11.5-11.9); however, four of eight weekly means were less than 10.7 for the m-Det group. Swentzel indicated that the reduction in number of implants was probably not genetic in origin, but speculated that based on a report by Gleiberman *et al.* (1976) the reduction may have been caused by reduced motility of spermatozoa or aspermia.

Tests with the bacterium *Salmonella typhimurium* in standard Ames plate assays were negative in strains TA98, TA100, TA1535, TA1537 and TA1538 at concentrations up to 1 µl/plate in the presence and absence of Aroclor® 1254-induced rat liver homogenate (Sauers *et al.*, 1981; Macko and Weeks, 1980). Sauers and coworkers noted that a concentration of 10 µl/plate was toxic to the bacterium.

Macko and Weeks (1980) also reported negative results for m-Det in a mutagenicity test with the yeast, *Saccharomyces cerevisiae*. The test concentrations were not specified.

Ficsor and Lo Piccolo (1972) tested Off® insect repellent (which contains 50% m-Det as the active ingredient) for its ability to revert two *Escherichia coli* lac^- mutants, NG422 and YA482, to the lactose-fermenting phenotype and for its ability to revert cys^- (*cys* B12) and two leu^- (AP517, 5BU504) auxotrophs to prototrophy in bacterial plate assays. Test results were negative.

- Reproductive Studies/Teratogenicity

Daily dermal application of a 75% solution of m-Det (in ethanol) to the backs of pregnant New Zealand white rabbits on day 1 through day 29 of gestation at dosages of 50, 100, 500 or 1000 mg m-Det/kg/day caused moderate to severe skin irritation but no teratogenic response. Dermal irritation including erythema, cracking and edema was seen in all rabbits in the 100, 500 and 1000 mg/kg groups by the seventh day of application. Similar irritation was noted after 14 days in the low dose group. Irritation persisted, increased in area and severity as the study progressed. No effect on body weight, fertility index, implantations/doe, number of fetuses/doe or histopathology were observed except for dose-related degrees of hyperkeratosis, parakeratosis and acanthosis of treated skin. Blood chemistries revealed dose-related increases in serum gamma glutamyl transpeptidase at days 7, 14, 21 and 30 days of gestation in the two highest treatment groups and in the 100 mg/kg group on day 14. Blood urea nitrogen levels were elevated at 30 days in the 500 and 1000 mg/kg groups. Fetal weight, length, placental weight and sex ratios were all within normal limits (Angerhofer and Weeks, 1981).

Lebowitz et al. (1981) examined the effects of m-Det on rat testes and gametes. Male rats (80/group) were exposed by dermal application of 0, 100, 300 or 1000 mg/kg/day of m-Det, 5 days/week for 9 weeks. Sperm samples were collected after 35, 65 and 95 days. No evidence of toxicity, reduced viability or sperm head abnormalities were observed. Small but significant weight changes were observed in kidneys and livers but no changes were noted in testicular histopathology or weight.

In contrast to these findings, reports in the Russian literature suggest embryotoxic and gonadotoxic effects for m-Det. Gleiberman et al. (1975) reported that fertility rates in pregnant rats treated daily throughout pregnancy with either 100 or 1000 mg/kg m-Det applied percutaneously were comparable to controls but that the rate of implantation was significantly reduced in the high dose group due to pre-implantational and post-implantational resorptions. Overall embryonal mortality was 20.9%, 27.6% and 34.1% for the control, 100 mg/kg and 1000 mg/kg groups, respectively. No teratogenic effect was observed. Postnatal mortality was 15.7%, 27.4% and 44.03%, respectively, and newborn rats showed retarded development. Residues of m-Det were detected in the ovaries, adrenals and brain tissue of dams killed on day 19 and rat fetuses (days 20-28) reportedly contained 230 µg m-Det/g brain tissue and 5.25 µg/g tissue in liver, heart, kidney and ovaries.

In a later report, Gleiberman et al. (1976) noted that regular application of m-Det to the skin of female, male and pregnant albino rats resulted in a reduction in the number of "yellow bodies" of pregnancy, inhibition of spermatozoid motility and an increase in the number of their pathological forms, increased embryonal and postnatal death rates, and a decrease in the size, body weight and retardation of development of offspring, the intensity of which was determined by dose and duration of application.

At variance with the observations made by Gleiberman et al., Snodgrass et al. (1980) found no detectable radioactivity in fetuses of rabbits given

repeated dermal applications of ^{14}C-labelled m-Det (75% in ethanol) throughout gestation. Species differences may partly explain the divergent findings.

Kuhlmann and coworkers (1981) reported that m-Det (1.27 µmol applied directly to the chorioallantoic membrane on day 2) produced teratologic and embryotoxic effects in chick embryos. Only 41% of the treated embryos survived to day 15 of incubation and 33% of day 15 embryos had gross malformations, primarily cardiovascular and musculoskeletal defects, which was a significantly higher rate than those noted for vehicle and untreated controls. However, the lack of anatomic and physiologic maternal-fetal relationships and the resultant ultrasensitivity of this test system render it unsuitable for assessing potential teratogenic risks in humans.

Metabolic Characteristics

The metabolic fate of m-Det has been studied in man, dog, mouse, rabbit and guinea pig. Most of the available information deals with percutaneous application which results in rapid absorption and elimination. The main route of elimination in all species examined is via the urine, with the bulk of the administered dose recovered within the first 24 hours. Fecal excretion is insignificant. There appears to be little difference in distribution and elimination of m-Det following either intravenous or percutaneous administration.

Two studies examined the metabolic pathway of intravenously administered m-Det in animals (Reifenrath et al., 1980; Blomquist et al., 1975). In hairless dogs given intravenous injections of ^{14}C-labelled m-Det (348 µg/dog), average urinary recovery was 90.6% of the injected dose, with insignificant amounts found in the feces. Most of the injected dose was recovered in urine within the first 24 hours. Radioactivity levels in blood fell to near background values between 4 to 8 hours after injection. (Reifenrath et al., 1980).

Blomquist and coworkers (1975), using whole body autoradiographic techniques, studied the tissue distribution of ^{14}C-labeled m-Det in NMRI mice. The mice were given intravenous injections of 15 mg m-Det/kg body weight. High tissue concentrations of administered radioactivity were found in the liver, kidney, lacrimal gland and nasal mucosa. Concentrations above blood levels were also noted in the thyroid and brown fat shortly after injection. Rapid excretion of the administered radioactivity took place via the kidney, with little radioactivity present in tissues at 4 hours except for a persisting tissue concentration in the lacrimal glands. Some 95.6% of administered radioactivity was recovered in urine during the first 8 hours; this figure rose to 97.3% by 40 hours. A trace amount (0.6%) was found in the feces. None was detected in expired air.

Reifenrath and coworkers (1980) reported rapid percutaneous penetration of an applied dose (0.32 mg/cm^2) of ^{14}C-labelled m-Det in 3 hairless dogs (9-13 kg). Urinary excretion was the major route of elimination (7.9 ± 2.5% of applied dose after 4-5 days), with insignificant amounts found in the feces. An additional 1% of the applied dose was recovered from the skin surface 48 hours after application. The majority of radioactivity (75.3 ± 4.6%) evaporated from the skin and was detected in a protective nonocclusive

patch. Levels of radioactivity in blood were too low to be accurately determined. A total of 83.7 ± 3.5% of the applied radioactivity was recovered.

In a subsequent study, Reifenrath et al. (1981) reported that the mean percentage dermal absorption in dogs decreased with increasing dose but that the difference was not statistically significant at the 95% confidence level (Student's two-tailed t test). The percentage penetration values were 9.4 ± 3.6% and 12.8 ± 4.6% for the 320 μg/cm² and 4 μg/cm² doses, respectively.

Rapid dermal penetration of m-Det has also been reported for guinea pigs, rabbits, rats and mice (Gleiberman and Voronkina, 1972; Lur'e et al., 1978; Snodgrass et al., 1980; Schmidt et al., 1959; Blomquist and Thorsell, 1977). In guinea pigs, between 18 and 48% of a dermal application of ^{14}C-labelled m-Det (7 mg/in²) was absorbed within 6 hours of application. An additional 14% of the dose was lost by evaporation for the skin, and 40-67% of the applied dose was recovered from the skin at 6 hours. Over 80% of the absorbed radioactivity was excreted in urine within 24 hours. By 8 days, some 93% of the absorbed dose was accounted for in urine and 0.75% in feces. Overall recovery was greater than 98% of the applied dose (Schmidt et al., 1959).

Snodgrass et al. (1980) measured the dermal penetration of ^{14}C-labelled m-Det in rats, rabbits and dogs. The area was covered with a nonocclusive protective patch. Absorption was quantitated by measuring radioactivity in urine for 7 days following the single dermal application (4 μg/cm²). Maximum penetration occurred rapidly in each species, with at least 75% of the absorbed dose appearing in urine within 24 hours. Elimination was essentially complete after 3-4 days. The percentage recovery of applied radioactivity for each species is presented in Table 2. No tissue regardless of animal species contained more than 1 ppb of radiocarbon/g.

TABLE 2

ELIMINATION OF RADIOACTIVITY AFTER PERCUTANEOUS APPLICATION OF [^{14}C]-m-DET IN THREE SPECIES

(% of Dose Administered)

Species	Urine	Feces	24 hr Patch	7 day Patch	Skin	Total
Rat (male)	43	0.4	28	4.0	6.7	82.1
Rat (female)	32	0.4	31	1.6	1.2	66.6
Rabbit (female)	36	2.3	22	6.7	15.0	81.9
Dog (male)	31	0.4	32	3.3	2.8	69.3

Taken from Snodgrass et al. (1980).

Tissue distribution and excretion patterns were similar in mice following dermal application of m-Det to those noted after intravenous administration (Blomquist and Thorsell, 1977). However, low level urinary

excretion (0.2% dose/day) persisted throughout a one month observation period. Some 16-26% of the applied radioactivity was found in the superficial layers of mouse skin at 36 days.

Gleiberman and Voronkina (1972) reported that skin absorption of m-Det in laboratory animals was retarded by reduced temperature or by the use of lotions containing alcohol or dimethyl phthalate. Once absorbed, however, m-Det was capable of penetrating hematoencephalic and placental barriers.

Two experiments with pregnant rabbits were conducted by Snodgrass and associates (1980). In the first experiment, they determined the distribution of ^{14}C-labelled m-Det in pregnant rabbits given a single intravenous injection on day 15 of gestation. Maximum distribution occurred 15 minutes after injection and elimination, though not a first order process, rapidly followed. The half-life for disappearance of radioactivity from circulating blood was 30 minutes. Fetuses had the lowest level of radioactivity of any specimen monitored, about six times lower than simultaneous blood levels.

The second experiment involved the repeated dermal application of ^{14}C-labelled m-Det (75% in ethanol) at dosages of 50, 100 or 500 mg/kg/day to pregnant rabbits from day 1 through day 29 of pregnancy. No evidence of bioaccumulation was observed in dams or fetuses at term. A steady-state absorption/elimination pattern of about 45% of each day's dose was seen. An additional 35% of the dose accounted for was unabsorbed. No detectable radioactivity was found in the fetuses (Snodgrass et al., 1980).

Human Data

Most of the available human metabolic data deal with percutaneous application. An abbreviated account of human intravenous administration, however, was noted by Feldmann and Maibach (1970). They reported a 52.3% recovery of radioactivity in the urine in man after intravenous administration of ^{14}C-Det, with a half-life of 4 hours. The number of test subjects and the duration of the urinary collection period were not stated.

Feldmann and Maibach (1970) also quantitated percutaneous penetration of ^{14}C-labelled m-Det applied to ventral forearm of four human volunteers by measurement of radioactivity in urine over a 5 day period. Application of m-Det (in acetone) at a level of 4 $\mu g/cm^2$, with the application site washed after 24 hours, resulted in skin penetration of 16.7 ± 5.1% of the total dose by 5 days. The maximum rate of absorption occurred during the first twelve hours (0.77% dose/hour) with the rate of penetration decreasing thereafter. Levels of radioactivity in urine fell to less than 0.3% of the applied dose after 5 days.

Blomquist and Thorsell (1977) reported on two experiments conducted with the same female volunteer in which 0.12 mg m-Det/kg body weight (in absolute ethanol) was applied to the forearm area. The treated area was washed with absolute ethanol 8 hours after application. In the two experiments, 5.5% and 3.3% of the applied radioactivity were recovered in the urine by 48 hours; an additional 8% and 15% of the applied radioactivity were recovered in the 8-hour washing solutions.

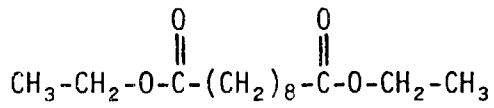
Some of the topically applied m-Det is also lost by evaporation from the skin surface. Spencer and coworkers (1979) found that 9.6% of an applied dose of 0.25 μg/cm² ^{14}C-Det evaporated from the treated forearm area of 8 volunteers during the first hour following application. In vitro studies with abdominal cadaver skin provided similar results (i.e., 9.7% evaporation after one hour at the same application rate).

Wu et al. (1979) characterized the metabolites of m-Det in the urine of a 30-year-old man who applied a commercial formulation containing m-Det to about 75% of his skin surface. Urine samples were collected over a 36 hour period, and a blood sample was drawn 8 hours post-application. Total exposure was calculated to be 133 mg m-Det/kg body weight. Unchanged m-Det was present in the urine for 18 hours post-exposure, and 0.3 mg% free m-Det was found in blood 8 hours after skin application. Wu and coworkers estimated that ~10-14% of m-Det was excreted unchanged in urine in the first hour, dropping to 2% by the fourth hour. Urinary metabolites consisted primarily of the glucuronide. There was also some evidence of the presence of a small amount of benzylic alcohol. It appears from these preliminary findings that oxidation of the benzylic moiety and hydroxylation of the side chain of m-Det are the predominant routes of metabolism in humans.

Monitoring and Detection

As noted in the Metabolic Characteristics section, unmetabolized m-Det was found in urine samples of the test subject for 18 hours after dermal exposure and in blood samples at trace levels. Approximately 10-14% of the applied m-Det was excreted in urine in the first hour (Wu et al., 1979).

A suitable analytical procedure for the m-Det in urine includes liquid/liquid extraction and subsequent analysis by gas chromatography with flame ionization detection (GC/FID). An aliquot of the sample is extracted into hexane. The hexane extract is then chromatographed on an OV101 capillary GC column or packed GC column. The gas chromatographic conditions necessary for resolution of the m-Det from interferences will need to be optimized. The detection limit for this procedure is estimated to be 2 ng injected on a column. If interferences cannot be resolved chromatographically, an alternative extraction clean-up procedure for m-Det involves a sequential liquid/liquid extract. A urine aliquot in sodium carbonate buffer (pH=8.2) is extracted with methylene chloride/ethyl alcohol (3:1 v/v). The pH of the aqueous phase is then adjusted to 13.0 with an ammonia buffer and reextracted with chloroform in butanal. The two organic extracts are then combined, dried through sodium sulfate and concentrated by evaporation (Prokofleva et al., 1978; Wu et al., 1979).

Simulant:	Diethyl Sebacate
Formula:	
CAS Reg. No.:	110-40-7
Molecular Weight:	258.36
Chemical State (20°C):	colorless to yellowish liquid
Liquid Density (g/cc):	d_4^{20} 0.965
Vapor Density (compared to air):	8.96 (Lyman et al., 1982)
Freezing/Melting Point (°C):	1-3°
Boiling Point (°C):	297° (Furia and Bellanca, 1975) ~307° with some decomposition (Stecher, 1968)
Flash Point (°C):	180°
Vapor Pressure (mm Hg at 20°C):	3.9×10^{-3} (Lyman et al., 1982 est. for 297°) 2.4×10^{-3} (Lyman et al., 1982 est. for 307°)
Volatility (mg/m^3):	34-55 (Lyman et al., 1982)
Viscosity (cp at 20°C):	18.3-21 (Lyman et al., 1982)
Odor:	Fruity
Action on Metals or Other Materials:	
Reference Source(s):	Furia and Bellanca (1975); RTECS (1980); Stecher (1968); Lyman et al. (1982); Clayton and Clayton (1981); Food Chemicals Codex (1981)

DIETHYL SEBACATE

Diethyl sebacate is a colorless to yellowish liquid. It has been used as a fragrance in commercial products and as a flavorant (Opdyke, 1978d). It was given GRAS status by the Flavor Extract Manufacturer's Association (1965) and has been cleared for use in foods under Section 172.515 of the Code of Federal Regulations (synthetic flavoring substances and adjuvants) (Food Chemical News Guide, 1982). The Council of Europe (1974) indicated that a level of 10 ppm diethyl sebacate may be added to foodstuffs without hazard to public health. Maximum concentrations of diethyl sebacate in commercial products are reported as 0.1% in soap, 0.01% in detergent, 0.03% in creams and lotions and 0.4% in perfumes; typical concentrations are approximately one order of magnitude less than these maximum concentrations (Opdyke, 1978d). Reported levels used in foods are 4.1 ppm in non-alcoholic beverages, 21 ppm in candy, 9.1 ppm in ice cream, 41 ppm in baked goods, 3.2-19 ppm in gelatins and puddings and 2.7-450 ppm in chewing gum (Furia and Bellanca, 1975). Diethyl sebacate has also been used in lipsticks, vanishing creams, skin and bathing oils and fabric softeners (Schneider, 1980).

Potential Health Effects

Human Data

No irritation to human skin was noted following a 48-hour closed patch test with 4% diethyl sebacate in petrolatum nor were any sensitization reactions noted in a maximization test with 25 volunteers with this concentration (Kligman, 1975).

Schneider (1980), however, reported induction of allergic contact dermatitis in two human subjects tested in patch tests with 20% diethyl sebacate in ethanol. Two additional cases were reported by Moss (1974) and Berlin and Miller (1976).

Diethyl sebacate was found to increase the absorption of the anti-inflammatory agent indomethacin from a pressure-sensitive adhesive topical composition. The rate of absorption of indomethacin by human skin was 29.4% from compositions with diethyl sebacate, compared to 12.6% from compositions without diethyl sebacate (Tamada et al., 1981).

No other data concerned with the effect of human exposure to diethyl sebacate were found.

Animal Studies

- Acute Toxicity

Acute oral LD_{50} values of 14.47 and 7.28 g/kg diethyl sebacate have been reported for rats and guinea pigs, respectively (RTECS, 1980). The acute dermal LD_{50} in rabbits was >5.0 g/kg (Levenstein, 1975).

Slight irritation was produced in rabbits following application of undiluted diethyl sebacate to intact or abraded skin for 24 hours under occlusion (Levenstein, 1975).

Addition of a mixture of 15% diethyl sebacate and 15% dimethyl sulfoxide to a conventional ointment significantly increased the penetration of salicylic acid and benzocaine from the ointment into rat skin *in vitro* (Sanchez de Rivera Vazquez and Rodriguez Perez, 1977).

- Subchronic Effects

No effects on growth, hematology or histopathology were noted in 2 groups of 5 male and 5 female Osborne-Mendel rats fed either 10,000 ppm in the diet for 17-18 weeks or 1000 ppm 27-29 weeks (Hagan *et al.*, 1967).

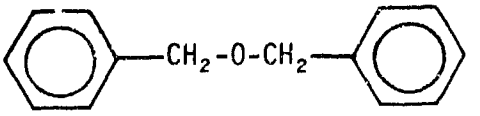
No other toxicity, carcinogenicity, mutagenicity or teratogenicity data were available for diethyl sebacate.

- Anti-tumor Activity

Diethyl sebacate was found to have significant inhibitory activity against transplantable AKR leukemia in mice. The average mouse survival rate was increased from 14 days in controls to 29 days following administration of 2.5 mmol/ml diethyl sebacate; 4/9 treated mice survived after 90 days. All mice treated with 5 mmol/ml diethyl sebacate survived after 90 days, compared to an average survival of 18 days for controls (Townsend *et al.*, 1962). In a similar study, diethyl sebacate gave partial protection against Gardner lymphosarcoma 6C3HED in mice following administration of a minimum concentration of 12.4 mM. However, this concentration of diethyl sebacate had no inhibitory effect against the ascites form of Ehrlich carcinoma or TA_3 mammary carcinoma (Tolnai and Morgan, 1962).

Monitoring and Detection

There are no methods reported in the literature for the analysis of diethyl sebacate in biological fluids. Gas chromatographic methods of analysis are reported for neat samples of the parent compound (0.5% silicone SE30 on hydrofluoric acid-etched beads or 0.5% neopentylglycol polysebacate on acid-etched beads) (Zulaica and Guiochon, 1963). The methods would have to be modified for analysis of saliva, urine or blood samples. The parent compound would probably be metabolized to the half-ester or dicarboxylic acid, and the metabolites possibly excreted as conjugates. A rapid visualization (spot) test for diethyl sebacate might include a colorimetric method.

Simulant:	Dibenzyl Ether
Formula:	
CAS Reg. No.:	103-50-4
Molecular Weight:	198.25
Chemical State (20°C):	colorless liquid
Liquid Density (g/cc):	d_4^{20} 1.001
Vapor Density (compared to air):	6.88 (Lyman et al., 1982)
Freezing/Melting Point (°C):	1.5-3.5°
Boiling Point (°C):	[illegible]°
Flash Point (°C):	135°
Vapor Pressure (mm Hg at 20°C):	4.2×10^{-3} (Lyman et al., 1982)
Volatility (mg/m³):	46 (Lyman et al., 1982)
Viscosity (cp at 20°C):	18.5 (Lyman et al., 1982)
Odor:	slightly earthy, mushroom-like with rosy undertone
Action on Metals or Other Materials:	
Reference Source(s):	RTECS (1980); Aldrich (1980); Stecher (1968); Lyman et al. (1982); Furia and Bellanca (1975)

DIBENZYL ETHER

Dibenzyl ether has not been reported to occur in nature. It was given GRAS status by the Flavor Extract Manufacturers' Association (1965) and has been approved for use in foods under Section 172.515 (synthetic flavoring substances and adjuvants) of the Code of Federal Regulations (Food Chemical News Guide, 1982). Reported levels of use include 8.3 ppm in non-alcoholic beverages, 5.6 ppm in ice cream, 23 ppm in candy, 25 ppm in baked goods, and 85-160 ppm in chewing gum. The Council of Europe (1974) listed dibenzyl ether among artificial flavoring substances that may be temporarily added to foodstuffs without hazard to public health. Dibenzyl ether is also used in various commercial products at maximum concentrations of 0.2% in soap, 0.01% in detergent, 0.03% in creams and lotions and 1.0% in perfumes; typical levels of use are approximately one order of magnitude less than these maximum concentrations.

Potential Health Effects

Human Data

No skin irritation was produced in individuals tested with 4% dibenzyl ether in petrolatum in a 48-hour closed-patch test (Kligman, 1974). Negative sensitization reactions were also reported with this same concentration in 25 individuals in a maximization test (Kligman, 1974).

Positive reactions were produced in 3/200 rubber workers patch-tested with 2% dibenzyl ether in Eucerin® (Schultheiss, 1959).

No other carcinogenic, teratogenic, mutagenic or long-term effects data were available for human exposure to dibenzyl ether.

Animal Studies

The acute oral LD_{50} for rats was reported as 2.5 g/kg and the acute dermal LD_{50} for rabbits was greater than 5 g/kg (Wohl, 1974).

Wohl (1974) observed that application of undiluted dibenzyl ether to intact or abraded rabbit skin for 24 hours under occlusion produced no irritation. However, RTECS (1980) reported that moderate irritation was produced in both skin and eyes of rabbits following topical application of 500 mg dibenzyl ether for 24 hours.

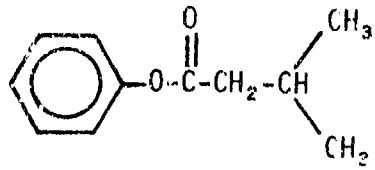
Marked epidermal thickening was induced in guinea pig skin following daily application of 10% dibenzyl ether in absolute alcohol for 8-10 days. A slight reaction was elicited by 2% dibenzyl ether (Schaaf, 1961).

No additional carcinogenic, teratogenic, mutagenic or long-term effects data were available for dibenzyl ether.

Monitoring and Detection

There are no methods reported in the literature for the analysis of dibenzyl ether in biological fluids. A gas chromatographic or high performance liquid chromatographic method of analysis would need to be

developed for the analysis of the parent compound in saliva, urine or blood samples. The parent compound would probably be eliminated either as the ether or metabolized to benzyl alcohol or other products as described in our first report for the use of benzyl alcohol as a simulant. A rapid visualization (spot) test for dibenzyl ether might include the use of ultraviolet light and a colorimetric method.

Simulant:	Isoamyl Benzoate
Formula:	
CAS Reg. No.:	94-46-2
Molecular Weight:	192.26
Chemical State (20°C):	colorless liquid
Liquid Density (g/cc):	d_4^{15} 0.993
Vapor Density (compared to air):	6.68 (Lyman et al., 1982)
Freezing/Melting Point (°C):	
Boiling Point (°C):	260-262°
Flash Point (°C):	>100°
Vapor Pressure (mm Hg at 20°C):	1.7×10^{-2} (Lyman et al., 1982)
Volatility (mg/m^3):	180 (Lyman et al., 1982)
Viscosity (cp at 20°C):	11.9 (Lyman et al., 1982)
Odor:	Fruity, slightly pungent
Action on Metals or Other Materials:	
Reference Source(s):	Furia and Bellanca (1975); RTECS (1980); Lyman et al. (1982); Stecher (1968)

ISOAMYL BENZOATE

Isoamyl benzoate is a colorless liquid with a fruity, slightly pungent odor. It is reported to occur in cherry oil. Isoamyl benzoate was granted GRAS status by the Flavor Extract Manufacturers' Association (1965) and has been cleared for use in foods under Section 172.515 (synthetic flavoring substances and adjuvants) of the Code of Federal Regulations (Food Chemical News Guide, 1982). An acceptable daily intake of 5 mg/kg of isoamyl benzoate is listed by the Council of Europe (1972). Levels of use include 3 ppm in non-alcoholic beverages, 2.5 ppm in ice cream, 3.5 ppm in candy, 7.4 ppm in baked goods, 4.6 ppm in gelatins and puddings and 200 ppm in chewing gum (Furia and Bellanca, 1975). Isoamyl benzoate is also used in commercial products at maximum reported levels of 0.09% in soap, 0.009% in detergents, 0.03% in creams and lotions and 0.6% in perfumes; typical use levels are approximately one order of magnitude less than these maximum levels (Opdyke, 1973).

Potential Health Effects

Human Data

Isoamyl benzoate produced no skin irritation in 25 individuals tested with a concentration of 6% in petrolatum in a 48-hour closed-patch test (Kligman, 1972).

No other data were available concerning potential health effects in humans resulting from exposure to isoamyl benzoate.

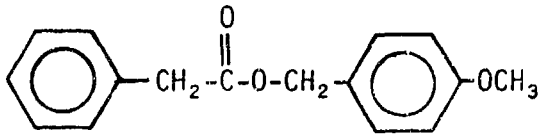
Animal Studies

The acute oral LD_{50} for isoamyl benzoate in rats was 6.33 g/kg. The acute dermal LD_{50} in rabbits was reported as >5 g/kg (Weir, 1971). Mild skin irritation was produced in rabbits following application of 500 mg isoamyl benzoate for 24 hours (RTECS, 1980) or undiluted isoamyl benzoate to intact or abraded skin (length of time not specified) (Weir, 1971).

No other data were available concerning potential carcinogenic, teratogenic, mutagenic or long-term toxic effects of isoamyl benzoate.

Monitoring and Detection

There are no methods reported in the literature for the analysis of isoamyl benzoate in biological fluids. Gas chromatographic methods of analysis are available for neat samples of the parent compound (25% silicone rubber SE-30 on Celite or 25% carbowax 20M on Celite) (van der Dool and Kratz, 1963). The methods would have to be modified for analysis of saliva, urine or blood samples. The parent compound would probably be metabolized to phenol and isovaleric acid, and the metabolites excreted in the form of conjugates. Although we have not done literature searches for these two probable metabolites, methods of analysis in biological matrices should be available for these well-known compounds. A rapid visualization (spot) test for isoamyl benzoate might include the use of ultraviolet light and a colorimetric method.

Simulant:	Anisyl Phenylacetate
Formula:	
CAS Reg. No.:	102-17-0
Molecular Weight:	256.3
Chemical State (20°C):	colorless, oily liquid
Liquid Density (g/cc):	1.15 (Lyman et al., 1982)
Vapor Density (compared to air):	8.88 (Lyman et al., 1982)
Freezing/Melting Point (°C):	
Boiling Point (°C):	370°
Flash Point (°C):	
Vapor Pressure (mm Hg at 20°C):	7.4×10^{-5} (Lyman et al., 1982)
Volatility (mg/m³):	1.04 (Lyman et al., 1982)
Viscosity (cp at 20°C):	26.6 (Lyman et al., 1982)
Odor:	anise and honey-like
Action on Metals or Other Materials:	
Reference Source(s):	Furia and Bellanca (1975); Lyman et al. (1982)

ANISYL PHENYLACETATE

Anisyl phenylacetate is a colorless oily liquid with an anise or honey-like odor (Opdyke, 1980). It has been approved for use in food as a synthetic flavoring substance and adjuvant under 21 CFR 172.515 (Food Chemical News Guide, 1982). The Council of Europe (1974) lists anisyl phenyl acetate among the artificial flavoring substances which may be added to foodstuffs at a level of 5 ppm without hazard to public health. Anisyl phenylacetate is also used as a fragrance in commercial products at maximum reported levels of 0.1% in soap, 0.01% in detergent, 0.03% in creams and lotions and 0.7% in perfume; typical concentrations of use are approximately one order of magnitude less than these maximum levels (Opdyke, 1980).

Potential Health Effects

Human Data

No irritation was produced in humans in a 48-hour closed-patch skin test with 12% anisyl phenylacetate in petrolatum (Kligman, 1977). No sensitization reactions were observed in 25 individuals in a maximization test with 12% anisyl phenylacetate in petrolatum (Kligman, 1977).

No other data were available concerning the effects of anisyl phenylacetate exposure in humans.

Animal Studies

Both the acute oral LD_{50} value in rats and the acute dermal LD_{50} value for rabbits are greater than 5 g/kg (Moreno, 1977). Mild irritation was seen in rabbits following application of undiluted anisyl phenylacetate to the intact or abraded skin for 24 hours (Moreno, 1977).

No data were available concerning the carcinogenicity, teratogenicity, mutagenicity or long-term effects of anisyl phenylacetate in laboratory animals.

Metabolic Characteristics

No specific data were available concerning the metabolism of anisyl phenylacetate. Williams (1959) reported that the ether link is relatively stable in substituted anisoles with a carboxyl group or a potential carboxyl group attached to the aromatic ring.

Monitoring and Detection

There are no methods reported in the literature for the analysis of anisyl phenylacetate in biological fluids. A gas chromatographic or high performance liquid chromatographic method would need to be developed for the analysis of the parent compound in saliva, urine or blood samples. The parent compound would probably be metabolized to phenylacetic acid and 4-methoxybenzyl alcohol, and the metabolites excreted in the form of conjugates. Methods of analysis would need to be developed for the

metabolites and for hydrolysis of any excreted conjugates. A rapid visualization (spot) test for anisyl phenylacetate might include the use of ultraviolet light and a colorimetric method.

Simulant:	n-Octadecanethiol
Formula:	$CH_3(CH_2)_{17}SH$
CAS Reg. No.:	2885-00-9
Molecular Weight:	286.57
Chemical State (20°C):	liquid
Liquid Density (g/cc):	d_4^{20} 0.8475
Vapor Density (compared to air):	9.94 (Lyman et al., 1982)
Freezing/Melting Point (°C):	29-31°
Boiling Point (°C):	~380° (Lyman et al., 1982)
Flash Point (°C):	185°
Vapor Pressure (mm Hg at 20°C):	1.2×10^{-5} (Lyman et al., 1982)
Volatility (mg/m^3):	0.19 (Lyman et al., 1982)
Viscosity (cp at 20°C):	61.7 (Lyman et al., 1982)
Odor:	Mild characteristic odor of thiols
Action on Metals or Other Materials:	May react with some rubbers, but effect should not be severe (K. Sidman, Arthur D. Little, Inc., personal communication)
Reference Source(s):	Aldrich (1980); Claytor and Clayton (1981); Lyman et al. (1982); NIOSH (1978b).

n-OCTADECANETHIOL

n-Octadecanethiol is a liquid with a mild characteristic odor of thiols. It is used as a polymerization conditioner, in organic synthesis and in tarnish-preventing agents. The recommended ceiling limit for any 15-minute exposure has been established at 5.9 mg/m^3 or approximately 0.5 ppm (NIOSH, 1978b).

Potential Health Effects

The data concerning human health effects or mammalian toxicity from exposure to octadecanethiol are limited to one skin-painting study in mice.

Undiluted octadecanethiol applied as 0.2 ml doses, every other day for 6 days (total dose, 500 mg) to the shaved backs of albino mice caused significant increases in the weight, thickness and level of Δ^5 cholesterol of the treated epidermis. Hyperplasia was also observed in the hair follicles, along with marked hyperkeratinization. In addition, a decrease in the level of epidermal Δ^7-cholesterol was found, and the sebaceous glands were no longer visible. Treatment with a lower dose (total dose 3 mg octadecanethiol in ether) applied over 6 days also caused significant epidermal hyperplasia and decreased Δ^7 cholesterol levels, but to a lesser degree than those elicited by the higher dose. Also, the sebaceous glands were intact and only slightly atrophied and hair follicles were normal at the lower dosage. Application of this lower concentration over 14 days (6 mg total) resulted in no significant epidermal hyperplasia and Δ^5 cholesterol levels of the epidermis and the sebaceous glands were essentially normal. However, the Δ^7 cholesterol in the epidermis remained at a reduced level (Brooks et al., 1957). These investigators point out that application of undiluted octadecanethiol at a dose of 500 mg produced changes in the epidermis and sebaceous glands similar to those seen following treatment with the carcinogen methylcholanthrene (1.2 mg) prior to the development of skin carcinomas, including induction of epidermal hyperplasia, destruction of the sebaceous glands and reduction of Δ^7-cholesterol levels. The diluted octadecanethiol caused the decrease in the Δ^7-sterol without visibly damaging the sebaceous glands.

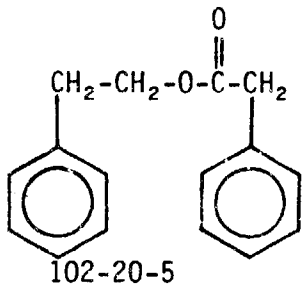
Metabolic Characteristics

Although no specific information concerning the metabolic fate of octadecanethiol was found, NIOSH (1978b) proposed the following scheme for alkane thiols, in general. The sulfur atom is metabolized by oxidation and excreted, for the most part, as urinary inorganic sulfate. In addition, methylation of the thiol followed by oxidation leads to excretions of some of the sulfur as the sulfone of the methylated thiol. The latter pathway appears to be more important for the higher molecular weight thiols. The sulfur atom is apparently not incorporated into cysteine or methionine sulfur in mammals. The thiols do not appear to be oxidized to disulfides in vivo, although this conversion takes place readily in vitro. It is possible that the thiols are maintained in the reduced state in vivo.

Monitoring and Detection

An excellent review of the information available on thiols was published by NIOSH (1978b). A NIOSH method is available for the analysis of butanethiol in air samples (NIOSH, 1978a). The traditional method for detection of thiols in biological fluids involves the use of Ellman's reagent (Burg et al., 1982). The analysis of such organosulfur compounds has also been reported from waste waters (Jenkins et al., 1980). The method uses gas chromatography coupled with a sulfur specific flame photometric detector, with sensitivity in the ppb (ml odorant/ml air) range.

Limited information is available on the metabolism and bioanalysis of alkane thiols. The thiols would probably be methylated, followed by oxidation, with the major excretion product being the sulfone of the methylated thiol. Analytical methods would need to be developed for the analysis of the parent thiol or methylated sulfone metabolite in urine samples. Gas chromatographic or high performance liquid chromatographic techniques should be suitable for this purpose.

Simulant:	Phenylethyl Phenylacetate
Formula:	
CAS Reg. No.:	102-20-5
Molecular Weight:	240.34
Chemical State (20°C):	crystalline; colorless to slightly yellow liquid above 26°
Liquid Density (g/cc):	1.12 at 30°
Vapor Density (compared to air):	8.33 (Lyman et al., 1982)
Freezing/Melting Point (°C):	28°
Boiling Point (°C):	325°
Flash Point (°C):	>100°
Vapor Pressure (mm Hg at 20°C):	9.6 x 10^{-5} (Lyman et al., 1982)
Volatility (mg/m^3):	1.3 (Lyman et al., 1982)
Viscosity (cp at 20°C):	13.8 (Lyman et al., 1982)
Odor:	Rosy, hyacinth-like
Action on Metals or Other Materials:	
Reference Source(s):	Furia and Bellanca (1975); Food Chemicals Codex (1981); RTECS (1980); Lyman et al. (1982)

PHENYLETHYL PHENYLACETATE

Phenylethyl phenylacetate is a colorless to slightly yellow-colored liquid, at temperatures above 26°C, with a rosy, hyacinth-like or sweet honey-like odor. It has not been reported to occur in nature (Opdyke, 1975). Phenylethyl phenylacetate was given GRAS status by the Flavor Extract Manufacturers' Association (1965) and has been approved for use in foods as a synthetic flavoring substance and adjuvant under 21 CFR 172.515 (Food Chemical News Guide, 1982). The Council of Europe (1974) cites a level of 10 ppm phenylethyl phenylacetate which may be added to foodstuffs without hazard to public health. Reported levels of use in various food products include 2.3 ppm in non-alcoholic beverages, 4.2 ppm in ice cream, 4.8 ppm in candy, 5.3 ppm in baked goods and 10 ppm in maraschino cherries (Furia and Bellanca, 1975). Phenylethyl phenylacetate is also used as a fragrance in commercial products at maximum reported concentrations of 0.15% in soap, 0.015% in detergent, 0.05% in creams and lotions and 0.2% in perfume; typical concentrations used in these products are approximately one order of magnitude less than these maximum levels (Opdyke, 1975).

Potential Health Effects

Human Data

No irritant effects were produced in humans following application of 2% phenylethyl phenylacetate in petrolatum in a 48-hour closed-patch test; sensitization reactions in a maximization test were also negative (Kligman, 1971) In 3 separate experiments, Majors (1971) and Blau and Kanof (1971) noted a similar absence of irritant and/or sensitization reactions in a total of 145 individuals tested with 2% phenylethyl phenylacetate in repeated insult patch-test procedures involving eleven 48-hour exposures.

No data were available on carcinogenicity, teratogericity, mutagenicity or long-term effects in humans exposed to phenylethyl phenylacetate.

Animal Studies

- Acute Toxicity

Jenner et al. (1964) reported an acute oral LD_{50} of 15.3 g/kg in rats. RTECS (1980) listed an acute oral LD_{50} value of 3.19 g/kg for both mice and guinea pigs. Similarly, Zaitsev and Rakhmanina (1974) reported acute oral LD_{50} values between 2.5 and 6.2 g/kg for rats, mice and guinea pigs.

- Subchronic Toxicity

Zaitsev and Rakhmanina (1974) indicated that no cumulative toxicity was apparent following oral administration of phenylethyl phenylacetate to rats, mice and guinea pigs. No doses or treatment regimes were given. These investigators also noted that phenylethyl phenylacetate and other phenylethyl alcohol derivatives increased the activity of alanine aminotransferase and sulfhydryl levels but decreased the activity of blood cholinesterase in rats following oral administration of 2% of the LD_{50} concentration.

No effects on growth, hematology or histopathology were observed in groups of 20 male and female Osborne-Mendel rats fed 1,000, 2,500 or 10,000 ppm phenylethyl phenylacetate in the diet for 17 weeks (Hagan et al., 1967).

No data were available concerning the carcinogenicity, teratogenicity or mutagenicity of phenylethyl phenylacetate in laboratory animals.

Monitoring and Detection

There are no methods reported in the literature for the analysis of phenylethyl phenylacetate in biological fluids. A gas chromatographic or high performance liquid chromatographic method would need to be developed for the analysis of the parent compound in saliva, urine or blood samples. The parent compound would probably be metabolized to 2-phenylalcohol and phenylacetic acid, and the metabolites excreted in the form of conjugates. Gas chromatographic methods of analysis have been reported for neat samples of 2-phenylethanol (40% Apiezow L on Celite) and phenylacetic acid (13% SE-30 on acid-washed Chromosorb W as the trimethylsilyl derivative) (Wehrli and Kovats, 1959; Hoffman et al., 1969; respectively). These methods would have to be adapted for analysis from a biological matrix and for hydrolysis of any excreted conjugate forms of the metabolites. A rapid visualization (spot) test for phenylethyl phenylacetate might include the use of ultraviolet light and a colorimetric method.

CONCLUSIONS

Dipentene (Supplement)

Dipentene meets the volatility, vapor pressure, boiling point, melting point and viscosity criteria for a volatile simulant. It is approved for use in foods by the Food and Drug Administration and is recognized as a GRAS substance by the Flavoring Extract Manufacturing Association.

Data presented in our earlier report (AFAMRL-TR-82-28) indicated the absence of tumorigenic and co-carcinogenic activity with benzo[a]pyrene for d-limonene in chronic dermal tests with mice. Acute and dermal LD_{50} values were reported to be in the 5 g/kg range and a study with dogs and rats suggested no apparent adverse effects following oral exposure to 1385 mg/kg/day for six months. Ingestion of a single 20 g dose by healthy human volunteers also produced no remarkable effects. Contact dermatitis was raised as a possible problem associated with the use of dipentene as a candidate simulant. Detection of glucuronide metabolites of dipentene in urine by thin layer chromatography was suggested.

Additional information on contact dermatitis associated with dipentene exposure was found for this report but did not resolve this issue. Several older studies implicated limonene as one of four possible constituents in turpentine responsible for the sensitization reactions. The sensitization response was found to be more severe with increasing degree of oxidation and the resultant increment in hydroperoxide content of the turpentine. As was the case for studies in our earlier report, these studies employed either formulations or dipentene with insufficient level of purity to establish firmly that dipentene, and not other terpene contaminants, is the causative agent.

A limited experiment conducted with two rabbits suggests no significant toxicity results from long-term exposure to dipentene fumes.

No mutagenic activity was observed with limonene in two standard Ames plate assays, and a negative pulmonary tumor response was observed in strain A mice.

Two studies reported the absence of morphologically transformed colonies in mammalian cell transformation systems exposed to limonene. This assay system was also used to study tumor promotion. Foci of transformed Rauscher murine leukemia virus-infected F344 rat embryo cells were observed following treatment with a subeffective dose of 3-methylcholanthrene and repeated exposure to limonene (1.5 µg/ml). Similarly treated cells exposed to a higher concentration of limonene (15 µg/ml) did not transform.

Tumor promoting activity was also reported for an 80% terpene fraction of expressed orange oil (~90% d-limonene) in a skin-painting study with strain 101 mice. After 33 weeks, there were 29 papillomas on 8 of 15 survivors compared to 1 papilloma on 1 of 16 controls. A squamous-cell carcinoma was found on one terpene-treated mouse during the 36th week of treatment. A second study also reported tumor promoting activity for an 80% citrus oil (consisting mainly of d-limonene) in Japanese SDDy-strain mice as well as Sprague Dawley rats. However, discrepancies between text and tables

in this publication raise questions as to its reliability. Because of the high doses used in these studies and the questionable relationship between induction of skin papillomas in mice and effects in humans, these results do not pose unusual toxicological problems for the use of dipentene as a volatile simulant.

Methyl Benzoate (Supplement)

Utilized both as a flavoran and a fragrance, methyl benzoate is approved for use in food by the Food and Drug Administration and is recognized as a GRAS substance by the Flavoring Extract Manufacturer's Association. An acceptable daily intake of 5 mg/kg methyl benzoate has been listed by the Council of Europe.

All its physical/chemical properties are within the established USAF criteria for a simulant of intermediate volatility.

Data presented in our earlier report were limited to observations of a lack of a sensitization response in human subjects, mild skin and eye irritation findings in rabbits and acute oral LD_{50} values in the 2 to 4 g/kg range.

Despite an intensive manual search of the older literature, scant information was found. A single study noted morphological changes in the mitral cells of the olfactory bulb in rats continuously breathing air containing 3×10^{-8} M methyl benzoate for 9 weeks.

Benzyl Alcohol (Supplement)

Benzyl alcohol is approved for use in synthetic food flavorings and adjuvants and is utilized extensively as a preservative and bacteriostat in parenteral pharmaceutical products. Benzyl alcohol meets all of the physical/chemical properties criteria for an intermediate volatility simulant except for a volatility slightly below the desired range.

Data presented in our earlier report indicated the lack of any chronic toxicity, mutagenicity and teratogenicity effects for this compound. Acute oral LD_{50} values were in the 1-2 g/kg range. Detection using gas chromatographic methods in plasma (or possibly saliva) was suggested..

The health effects data presented in this report support the general low level of risk associated with exposure to benzyl alcohol. Long term oral administration of benzyl alcohol (300 mg/kg) to rats for 3 months produced no apparent adverse effects, and several older studies noted the uneventful use of benzyl alcohol-containing products in the treatment of various human disorders. Injection of undiluted benzyl alcohol into chicks did produce embryonic anomalies. However, the high incidence of lethality and poor correlation of this test system to the in vivo human situation render the results unsuitable for evaluation of risk. A negative mutagenic response was recorded for benzyl alcohol in an Ames assay spot test.

Dimethyl Methylphosphonate

The vapor pressure, volatility, boiling point and viscosity of dimethyl methylphosphonate at 20°C are all within the established criteria for a volatile simulant. The flash point (43°C) may be somewhat low for dissemination by an explosive device.

The available information on dimethyl methylphosphonate in the published literature is scant. A single oral LD_{50} value of greater than 150 mg/kg in the rat was found. This value is considerably below the criterion established by the USAF.

Signs of ataxia were noted in hens injected intraperitoneally with 50 mg/kg dimethyl methylphosphonate daily for 10 days, but no delayed neurotoxic activity was observed.

Negative mutagenic activity was reportedly observed with this compound in an Ames assay.

This compound is currently being tested for carcinogenic activity in B6C3F1 mice and F344 rats by the National Toxicology Program; 90-day subchronic studies have been completed. Greater than 90% mortality occurred in mice given 4000 or 8000 mg/kg dimethyl methylphosphonate 5 days per week by gavage. All mice given 250, 500, 1000 or 2000 mg/kg survived. No microscopic changes were attributable to dimethyl methylphosphonate treatment, nor could the high mortality in the two highest dose groups be explained by histopathological findings. In a similar study conducted with F344 rats, test animals were administered 250, 500, 1000, 2000 or 4000 mg/kg dimethyl methylphosphonate by gavage 5 days per week for 13 weeks. All rats in the highest dose group died within one week and approximately 50% of the 2000 mg/kg group died during the course of the study. Increased liver to body weight ratios were recorded at necropsy for the 2000 mg/kg group. Histopathological lesions were observed in kidney, salivary glands and testes.

It is unknown whether dimethyl methylphosphonate is metabolized in man. An appropriate analytical technique for the parent compound in urine would include liquid/liquid extraction and gas chromatography with flame photometric detection.

n-Dodecanethiol

n-Dodecanethiol is used in the chemical synthesis of pharmaceuticals, insecticides, fungicides, non-ionic detergents and bacteriocides. An estimated 12,500 workers are exposed to dodecanethiol annually in the U.S. NIOSH has established 4.1 mg/m^3 as the recommended ceiling limit value for any 15 minute exposure to this material.

The two reported boiling points for dodecanethiol are within or slightly below the lower limit established for volatile simulant candidates, while the vapor pressure and volatility are higher than the established range. Other physical/chemical parameters are within acceptable ranges.

An acute oral LD_{50} value of 4.2 g/kg was found in mice while no lethalities occurred in rats ingesting 7 g/kg. A 20% concentration in acetone was reported to possess intense contact sensitizing ability in guinea pigs (50% of the animals developed dermatitis with a single application), raising the possibility of delayed dermatitis in exposed humans.

Subchronic inhalation exposure to 3400 mg/m^3, 4 times per week, induced no apparent effects in rats at 2 months, but by 5.5 months, leucocytosis, a 50% drop in adrenal function and reduced liver function were seen. Histopathological findings included mild bronchitis, hemorrhagic lungs and adrenals, slight fatty infiltration of the liver, myocardial fibrosis and slight brain edema.

An increased frequency of chromosomal aberrations was seen in workers exposed to vapors of a polychloroprene latex containing dodecanethiol. However, the contribution of the dodecanethiol to the observed response is difficult to assess in the absence of other supporting data.

Both dodecanethiol and a neoprene resin containing decanethiol used in the shoe industry induced positive, dose-related allergic responses in closed patch tests in individuals with shoe contact dermatitis. Irritant, but no sensitization reactions, were observed in more than 50% of healthy controls treated with 1% dodecanethiol in closed patch tests. No irritation was seen with this concentration in open patch tests.

Gas chromatographic or high performance liquid chromatographic techniques would be suitable techniques for analysis of the parent thiol or methylated sulfone metabolites in urine.

Methyl Salicylate

Methyl salicylate is widely used in the perfume and food industries, as well as medicinally in the form of analgesic/anti-inflammatory ointments and linaments. The Food and Drug Administration proposed tolerances for methyl salicylate ranging from 50 ppm in ice cream to 3300 ppm in chewing gum. A joint FAO/WHO committee on food additives cited on acceptable daily intake of up to 500 µg/kg body weight.

The boiling point, vapor pressure, volatility, melting point, flash point and viscosity at 20°C are all within the established range for a simulant of intermediate volatility.

Methyl salicylate is rapidly absorbed through skin or by ingestion. Ingestion of a 30 ml dose (~0.5 g/kg) may be fatal to adults. It is a dermal and mucous membrane irritant and caution should be taken to avoid ocular contact.

Reported oral LD_{50} values range between 700 and 2000 mg/kg for a number of laboratory species; a dermal LD_{50} of greater than 5000 mg/kg has been recorded for rabbits.

A number of subchronic and chronic studies have been conducted with methyl salicylate. Growth retardation but no other gross or microscopic abnormalities were noted in rats fed 10,000 ppm methyl salicylate in the diet

for 17 weeks; no effects were seen at the 1000 ppm level. A second study indicated an excess of cancellous (i.e., spongy) bone tissue in the femurs and tibias of rats fed 11,250 ppm in the diet for 10 weeks. This effect was not apparent in rats similarly exposed to 9000 ppm methyl salicylate. In a two-year feeding study, rats given 10,000 ppm methyl salicylate in the diet exhibited growth retardation and a slight excess of cancellous tissue in bone. This latter effect was also noted in the 5000 ppm group but not at the 1000 ppm level. Rats fed 20,000 ppm methyl salicylate died within 49 weeks; pneumonia was the only gross lesion observed.

No adverse effects were noted for dogs given capsules containing 250 mg/kg methyl salicylate daily, 6 days/week for 59 days; dogs treated with a higher dosage (500 mg/kg) died within one month.

Dermal application of 0.5-2 ml/kg/day to rabbits, 5 days per week for 96 days resulted in slight dermatitis, mild hepatitis and an increased incidence of spontaneous nephritis; application of 4 ml/kg/day produced death within 28 days.

No signs of toxicity were reported for rats given twenty 7 hour inhalation exposures to saturated methyl salicylate vapor (~700 mg/m^3).

Increased incidences of teratogenic effects have been induced in rats and hamsters exposed to methyl salicylate, but the administered doses approached levels which were lethal to the embryo and toxic to the dams (equivalent to a human dose of 30 g/60 kilo woman). To our knowledge, congenital malformations attributable to methyl salicylate or salicylate intake by pregnant women have not been reported.

An apparent dose-related response, starting at 1500 ppm, in average litter size, number of live-born progeny and number of day 4 survivors was seen in rats fed 500, 1500, 3000 or 5000 ppm methyl salicylate in diet for 3 generations, but no other evidence of toxicity or grossly visible abnormalities were observed.

Available carcinogenicity information is limited to findings of a negative pulmonary tumor response observed in strain A mice. No mutagenicity data was available.

Analysis of methyl salicylate exposure could be achieved in plasma or urine by high performance liquid chromatography of either salicylic or salicyluric acid. The assay is sensitive to 0.5 µg/ml for both compounds. Military personnel, however, would have to abstain from use of aspirin and other salicylates prior to military training exercises to avoid interference in detection. A possible spot test might include use of uv light and 5% aqueous ferric chloride spray (greenish-blue color) to detect salicylate esters.

Butyl Salicylate

The vapor pressure, volatility and viscosity of butyl salicylate at 20°C are all within acceptable criteria ranges for a candidate simulant in the low volatility range. The boiling point is low (268°C vs. +300°C). No melting point or flash point was found.

Butyl salicylate is used as a flavorant in foods and holds GRAS status from FEMA. The Council of Europe cites the addition of 0.5 ppm to foodstuffs as presenting no hazard to public health.

Human exposure data are limited to a negative skin irritation/skin sensitization study.

Undiluted butyl salicylate was also found to be non-irritating to rabbit skin. The oral LD_{50} value for this compound in rats is 1.7 g/kg. A dermal LD_{50} value of greater than 5 g/kg was recorded for rabbits.

Metabolic data for butyl salicylate were not found but based on available information for methyl salicylate, one would expect butyl salicylate to be hydrolyzed to butyl alcohol and salicylic acid. Monitoring and detection procedures would be the same as those noted for methyl salicylate.

Diethyl Toluamide

Solutions of 50-75% diethyl-m-toluamide (m-Det) are widely used as an insect repellant (e.g., Off®) which is applied directly to skin and/or clothing. The vapor pressure, volatility and viscosity of m-Det all fall within the criteria guidelines for a low volatility simulant. The boiling point is slightly below the established range (288-292° vs. +300°C). No flash or melting point values were found.

Available human data deal with short-term dermal contact or accidental ingestion by children. Continuous, 21-day, open patch tests with 50% m-Det produced no skin irritation, but similar occlusive patch tests with concentrations of 1-80% m-Det resulted in skin irritation, with severity a function of concentration. Two instances of human hypersensitivy to m-Det were also found in the literature.

Seven cases of toxic encephalopathy are associated with m-Det exposure. All these cases, however, occurred in females who are known or suspected to be deficient in the liver enzyme ornithine carbamoyltransferase, a sex-linked condition which is lethal to males.

Acute oral LD_{50} values range between 1585 to 3290 mg/kg. Dermal LD_{50} values are in the 4000-5000 mg/kg range. An inhalation LC_{50} of 5860-6000 mg/m^3 was reported for rats. Det is generally classified as a mild irritant in skin irritation studies. There are no indications that m-Det is a skin sensitizer. It is, however, an ocular irritant producing moderate to marked edema, lacrimation, conjunctivitis, pus and varying degrees of corneal injury. Flushing the eye after instillation decreased the irritation response.

No data on carcinogenicity were found, and there is no evidence to suggest any mutagenic activity for m-Det. A dominant lethal assay with mice, an Ames assay and a number of bacterial assays were all negative.

Reports in the Russian literature suggest embryotoxic and gonadotoxic effects for m-Det. At variance with these reported observations, U.S.

studies report no evidence of reduced viability or sperm head abnormalities in rats dermally exposed to 1000 mg/kg/day for 9 weeks.

In addition, no teratogenic response was noted in rabbits given daily dermal applications of 75% m-Det at dosages up to 1000 µg/kg/day throughout gestation.

Subchronic oral administration (0.3 ml/kg/day) to dogs for 13 weeks produced mild CNS stimulation and occasional emesis. Histopathological findings were within normal ranges. In a study with rats fed 0.01, 0.05, 0.1, 0.5 or 1% m-Det in the diet for 200 days, no significant effects on growth, mortality or food consumption were observed.

In 90 day dermal studies with dogs (0.3 ml/kg/day) and rabbits (0.5-3 ml/kg/day), moderate to severe skin irritation but no systemic toxicity was seen.

Rats exposed 8 hours/day, 5 days/week for 7 weeks to air saturated with m-Det exhibited no significant toxic effects.

Det is rapidly absorbed and eliminated, mainly in the urine within the first 24 hours. Fecal excretion is insignificant. Both unchanged m-Det and glucuronide metabolites are found in human urine. A suitable analytical procedure for m-Det in urine might include liquid/liquid extraction and analysis by gas chromatography with flame ionization detection.

Diethyl Sebacate

Diethyl sebacate is used as a fragrance in cosmetics and as a flavorant in foods It has GRAS status by FEMA and is approved for use in foods by the Food and Drug Administration. Reported use levels in foods range from 3-450 ppm. The Council of Europe has indicated that a level of 10 ppm may be added to foodstuff without hazard to human health. All the physical/chemical properties of diethyl sebacate are within acceptable ranges for a low volatility simulant.

Skin irritation and sensitization tests with human volunteers are negative. However, a few isolated cases of allergic contact dermatitis are contained in the published literature.

Animal studies indicate oral LD_{50} values between 7 and 14 g/kg. A dermal LD_{50} value of >5g/kg was recorded in rabbits. Slight skin irritation was seen in rabbits with undiluted diethyl sebacate after 24 hours under occlusion.

No adverse effects were noted in rats fed 10,000 ppm diethyl sebacate in the diet for 17-18 weeks or in rats fed 1000 ppm for 27-29 weeks.

No chronic toxicity, carcinogenicity, mutagenicity or reproductive toxicity information was found.

Gas chromatographic methods for analysis of neat samples of diethyl sebacate would have to be modified for analysis of the compound in biological fluids.

Dibenzyl Ether

The volatility, vapor pressure, boiling point, flash and melting points and viscosity of dibenzyl ether all fall within established criteria for simulants of low volatility.

Dibenzyl ether is approved for use in foods as a flavorant by the Food and Drug Administration and was granted GRAS status by FEMA. Reported levels of use in foods range from 5 to 160 ppm.

Skin irritation/sensitization studies in humans were negative. No other human exposure data were found.

An oral LD_{50} value of 2.5 g/kg was reported for rats. A dermal LD_{50} greater than 5 g/kg was observed with rabbits. Multiple reports indicate none to moderate skin irritation for dibenzyl ether in laboratory animals.

Gas chromatographic or high performance liquid chromatography methods would need to be developed for analysis of dibenzyl ether in biological fluids.

Isoamyl Benzoate

An acceptable daily intake of 5 mg/kg isoamyl benzoate is listed by the Council of Europe. It has been cleared by the FDA for use in foods and was granted GRAS status by FEMA. Reported levels of use in foods range from 2.5 ppm in ice cream to 200 ppm in chewing gum.

The vapor pressure, volatility, flash point and viscosity values are all within acceptable ranges. The boiling point is somewhat below (260° vs. +300°C) established limits.

Human exposure data are limited to a negative skin irritation study.

An acute oral LD_{50} of 3.3 g/kg was reported for rats. The dermal LD_{50} in rabbits was > 5g/kg. Mild skin irritation was seen in rabbits following a 24 hours exposure to 500 mg isoamyl benzoate. No information on carcinogenicity, mutagenicity, reproductive effects or chronic exposure was found.

Although no specific data on the metabolic fate of isoamyl benzoate were found it is probably metabolized to phenol and isovaleric acid, with metabolites excreted in the form of conjugates in the urine. Gas chromatographic methods are available for detection of neat samples of the parent compound. They would have to be modified for analysis in biological samples. A spot test might include UV light and a colorimetric method.

Anisyl Phenylacetate

Approved for use in foods as a flavorant, the Council of Europe lists anisyl phenylacetate among artificial flavoring substances which may be added to foodstuffs at a level of 5 ppm without hazard to human health.

The vapor pressure, volatility and boiling point of anisyl phenylacetate meet established criteria for a non-volatile simulant. Its viscosity at 20°C is slightly above (26 vs. <20 cp) the established range. No melting point or flash point was found.

Human exposure data are limited to a negative skin irritation/sensitization study. Oral and dermal LD_{50} values in rabbits are >5 g/kg. Mild skin irritation was noted in rabbits with undiluted material. No long-term exposure studies were found.

Specific metabolic data were not found, but anisyl phenylacetate would probably be metabolized to phenylacetic acid and 4-methoxybenzyl alcohol. The metabolites would be excreted in the form of conjugates in urine.

A gas chromatographic or high performance liquid chromatographic method would need to be developed for analysis of anisyl phenylacetate in saliva, blood or urine samples. A rapid visualization test for this compound might include the use of UV light and a colorimetric method.

n-Octadecanethiol

Although utilized industrially, no human exposure data were found for n-octadecanethiol. NIOSH has recommended a ceiling limit for any 15 minute exposure to 5.9 mg/m³. Health effects data are limited to a skin painting study in mice in which dermal application of undiluted octadecanethiol produced epidermal hyperplasia and marked hyperkeratinization.

The boiling point, vapor pressure, volatility and flash point are all within established ranges for a non-volatile simulant. The viscosity (62 vs. <20 cp) and melting point (30 vs. <15°C) are both outside established ranges for these two parameters.

Limited information is available on the metabolism of alkane thiols, but octadecanethiol would probably be methylated followed by oxidation, with the major excretion product being the sulfone of the methylated thiol. Analytical methods would have to be developed for the analysis of the parent compound or its methylated sulfone metabolite in urine.

Phenylethyl Phenylacetate

Phenylethyl phenylacetate is approved for use as a flavorant in foods by FDA and was granted GRAS status by the Flavoring Extract Manufacturer's Association. The Council of Europe cites a level of 10 ppm phenylethyl phenylacetate which may be added to foodstuffs without hazard to public health.

The vapor pressure, boiling point, flash point and viscosity are all within established ranges for a nonvolatile simulant. The volatility is slightly above the established range (1.3 vs. 1 mg/m³) The melting point (28°C) is also above 15°C. This material also has the limitation of being a liquid only above 26°C.

The only human data found were skin irritation/sensitization studies which were negative. Reported oral LD_{50} values for rats, mice and guinea

pigs range between 2.5 and 15.3 g/kg. No adverse effects were observed in rats fed up to 10,000 ppm in diet for 17 weeks. No carcinogenicity, mutagenicity, reproduction or chronic toxicity studies were found. The metabolic fate has apparently not been studied but phenylethyl phenylacetate would probably be metabolized to 2-phenylalcohol and phenylacetic acid, with the metabolites excreted in urine in the form of conjugates.

A gas chromatographic or high performance liquid chromatographic method would need to be developed for analysis of this material in saliva, urine or blood samples. Possible spot tests might include use of ultraviolet light and a colorimetric method.

RECOMMENDATIONS

In the course of this and an earlier task (Report No. AFAMRL-TR-82-28), eighteen candidate simulants have been proposed. All meet the majority of physical/chemical criteria established by the USAF. Therefore, selection of the most appropriate candidates within each volatility category is contingent upon the adequacy of available toxicological information. The status of available toxicological data for the eighteen candidate simulants is indicated in Table 3. Summaries of the toxicological findings for humans, acute toxicity in laboratory animals and long-term, metabolic and special studies findings are presented in Tables 4, 5 and 6, respectively.

Analysis of this information reveals that major gaps exist in the data bases for all the candidates. The preponderance of human exposure data deal with skin irritation/sensitization studies which do not appear to be of concern except for possible contact dermatitis with dipentene exposure. There are no human inhalation data and animal inhalation data are available for only four candidates (butanethiol, hexanethiol, benzyl alcohol, diethyl toluamide).

Acute oral LD_{50} values are acceptable for all candidates except for dimethyl methylphosphonate whose value is an order of magnitude below the acceptable limit. Acceptable dermal LD_{50} values are available for dimethyl sulfoxide, dipentene, benzyl alcohol, methyl salicylate, all of the low volatility candidates and anisyl phenylacetate. Long-term exposure data are available for dimethyl sulfoxide, dipentene, benzyl alcohol, methyl salicylate and diethyl toluamide.

None of the candidates appear to present problems with respect to carcinogenic or mutagenic activity but data are severely lacking in these areas. Positive teratogenic findings were noted for dimethyl sulfoxide, benzyl alcohol and methyl salicylate, but only with very high doses that were toxic to both dams and embryos.

The metabolic pathways are known for dimethyl sulfoxide, dipentene, benzyl alcohol, methyl and butyl salicylate and diethyl toluamide. Detection of any of these compounds in biological fluids is possible.

Based on this analysis, the most documented candidates within each volatility category include dimethyl sulfoxide (V), dipentene (V), benzyl alcohol (I), methyl salicylate (I), diethyl toluamide (L) and anisyl phenylacetate (NV). In our best judgement, an adequate level of toxicological information is available to recommend these compounds as candidate simulants.

However, we do suggest that additional contemporary acute and subchronic (at least 30 day exposure) inhalation studies be carried out on the simulants selected for trial, since the majority of this type of data on these compounds was generated many years ago. In addition, repeated exposure dermal toxicity studies would be suitable for candidates in the intermediate, low and non-volatile classes. Among these, only diethyltoluamide has a reasonable data base in this area.

TABLE 3

STATUS OF AVAILABLE TOXICOLOGICAL DATA FOR EIGHTEEN CANDIDATE SIMULANTS

Candidates	Acute Oral LD_{50}	Acute Dermal LD_{50}	Acute Inhalation LD_{50}	Irritation Skin	Irritation Eye	CHO Gene Mutation-HGPRT	Chromosome Aberration/SCE	Mammalian Cell Transformation	Ames Assay
Volatile Category									
Dimethyl sulfoxide*	+	+		+	+				
Dipentene	+	+		+					
Butanethiol*	+		+	+	+			+	+
Hexanethiol*	+		+		+				
Dimethyl methyl-phosphonate	+								
n-Dodecanethiol	+			+			+?		
Intermediate Category									
Methyl benzoate*	+			+	+				
Benzyl alcohol*	+	+	+	+	+				
Octanoic acid*	+								+
Methyl Salicylate	+	+		+					
Low Category									
Butyl salicylate	+	+		+					
N,N-Diethyl-m-toluamide	+	+	+	+					+
Diethyl sebacate	+	+		+	+				+
Dibenzyl ether	+	+		+					
Isoamyl benzoate	+	+		+					
Non-volatile category									
Anisyl phenylacetate	+	+		+					
n-Octadecanethiol									
Phenylethyl phenylacetate	+			+					

* Data were presented in an earlier Arthur D. Little, Inc. report (AFAMRL-TR-82-28) to the USAF.

TABLE 4

SUMMARY OF AVAILABLE HUMAN EFFECTS DATA FOR EIGHTEEN CANDIDATE SIMULANTS

Candidates	Route of Exposure			
	Ingestion	Inhalation	Dermal	Ocular
Volatile Category				
Dimethyl sulfoxide			45 ml·14 days no effect	no effect
Dipentene	20 g p.o. - no effect		contact dermatitis?	
Butanethiol		toxicity at 50 ppm		
Hexanethiol				
Dimethyl methyl-phosphonate				
n-Dodecanethiol				
Intermediate Category				
Methyl benzoate			no effect	no effect
Benzyl alcohol			slight irritant	
Octanoic acid	1 g/kg - metabolic changes			
Methyl salicylate	30 ml - lethal		irritant	irritant
Low Category				
Butyl salicylate			no effect	
N,N-Diethyl-m-toluamide			no effect	
Diethyl sebacate			no effect	
Dibenzyl ether			no effect	
Isoamyl benzoate				
Non-volatile Category				
Anisyl phenylacetate			no effect	
n-Octadecanethiol				
Phenylethyl phenyl-acetate			no effect	

TABLE 5

SUMMARY OF AVAILABLE ACUTE TOXICITY INFORMATION FOR EIGHTEEN CANDIDATE SIMULANTS

Candidates	Acute Oral LD_{50} (rat) mg/kg	Dermal LD_{50} (rabbit) mg/kg	Acute Inhalation LC_{50} (rat)	Irritation Reported in Animals	
				Skin	Eye
Dimethyl sulfoxide	19700	>11000 (dog)		+	+
Dipentene	5300	>5000		+	
Butanethiol	2574 ppm		4460 ppm	-	+
Hexanethiol	1580		1200 ppm		-
Dimethyl methyl-phosphonate	>150				
n-Dodecanethiol	>7000			+	
Intermediate Category					
Methyl benzoate	2000-4000			+	+
Benzyl alcohol	1230-3200	2000	10000 ppm/8hr	+	+
Octanoic acid	10000				
Methyl salicylate	887-1250	>5000		+	+
Low Category					
Butyl salicylate	1700	>5000		-	
N,N-Diethyl-m-tolua-mide	2000-3290	4340	5860-56000 mg/m^3	+	+
Diethyl sebacate	14470	>5000		+	+
Dibenzyl ether	2500	>5000		+	+
Isoamyl benzoate	6330	>5000		+	
Non-volatile Category					
Anisyl phenylacetate	>5000	>5000		+	
n-Octadecanethiol				+	
Phenylethyl phenyl-acetate	15300				

TABLE 6

SUMMARY OF AVAILABLE METABOLIC, LONG TERM EXPOSURE AND SPECIAL STUDIES FOR EIGHTEEN CANDIDATE SIMULANTS

Candidates	Metabolism	Long-term Exposure (NOAEL)*	Carcinogenicity	Mutagenicity	Teratogenicity Reproduction
Volatile Category					
Dimethyl sulfoxide	+	200 mg/m³·30 da inh (rat); 11 g/kg·6 mo. skin (monkey)		Neg.	Positive at toxic doses
Dipentene	+	1385 mg/kg oral (dog, rat)	Negative skin Transformation (+)	Neg.	
Butanethiol					
Hexanethiol					
Dimethyl methyl-phosphonate		2000 mg/kg p.o., 3 mo. (mouse)	In progress	Neg.	
n-Dodecanethiol		<3400 mg/m³ inh (rat)		?	
Intermediate Category					
Methyl benzoate					
Benzyl alcohol	+	300 mg/kg oral·3 mo (rat)			Positive chick eggs
Octanoic acid	+				
Methyl salicylate	+	1000 ppm diet (rat) 700 mg/m³ inh (rat)	Negative pulmonary response mice		Positive at toxic doses
Low Category					
Butyl salicylate	+				
N,N-Diethyl-m-toluamide	+	1% diet (rat) saturated air/inh (rat)·7 wk		Neg.	Negative USA Positive USSR
Diethyl sebacate		10,000 ppm dieth (rat)			
Dibenzyl ether					
Isoamyl benzoate					
Non-volatile Category					
Anisyl phenylacetate					
n-Octadecanethiol			Hyperplasia - skin painting		
Phenylethyl phenyl-acetate		10,000 ppm diet (rat)			

* NOAEL = No observed apparent effect level

APPENDIX A

EVALUATED CANDIDATES ELIMINATED FOR LACK OF TOXICOLOGICAL DATA

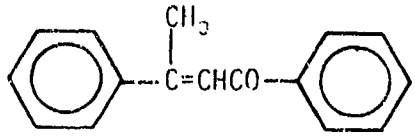
INTERMEDIATE

Simulant:	Dihexyl Ether	N-Aminopropylmorpholine;
Formula:	$C_6H_{13}OC_6H_{13}$	$C_2H_4OC_2H_4NC_3H_6NH_2$
CAS Reg. No.:	112-58-3	123-00-2
Molecular Weight:	186.34	144.21
Chemical State (20°C):	liquid	liquid
Liquid Density (g/cc):	0.794	d_{20}^{20} 0.9872
Vapor Density (compared to air):	6.4	4.97
Freezing/Melting Point (°C):	-43°	-15°
Boiling Point (°C):	226.4°	224.7°
Flash Point (°C):	77°	104°
Vapor Pressure (mm Hg at 20°C):	0.07 at 25°	0.06 (Sax, 1979) 0.01 (Clayton and Clayton, 1981)
Odor:		
Toxicity:	Oral LD_{50} (rat): 30.9 g/kg Dermal LD_{50} (rbt): 6.9 g/kg Intravenous LD_{100} (mus): 4.75 x 10^{-3} mol/kg Intravenous ED_{100} (mus): 3.43 x 10^{-3} mol/kg (loss of righting reflex) Skin irritant (rbt): 10 mg occluded 24 hr - severe; 500 mg unoccluded - mild Eye irritant (rbt): 500 mg	Oral LD_{50} (rat): 3.56 g/kg Dermal LD_{50} (rbt): 1.23 g/kg Skin irritant (rbt): 10 mg occluded 24 hr - severe; 500 mg unoccluded - severe Eye irritant (rbt): 1 mg
Reference Source(s):	Hoy, 1970; Jeppsson, 1975; RTECS, 1980; Sax, 1979	Clayton and Clayton, 1981; RTECS, 1980; Sax, 1979

INTERMEDIATE

Simulant:	N-(2-Hydroxyethyl)morpholine
Formula:	$C_6H_{13}NO_2$
CAS Reg. No.:	622-40-2
Molecular Weight:	131.18
Chemical State (20°C):	colorless liquid
Liquid Density (g/cc):	1.071
Vapor Density (compared to air):	4.54
Freezing/Melting Point (°C):	1.6°
Boiling Point (°C):	226°
Flash Point (°C):	99° (open cup)
Vapor Pressure (mm Hg at 20°C):	0.1
Odor:	
Toxicity:	Oral LD_{50} (rat): 12 g/kg Dermal LD_{50} (g.pg.): 2.5 g/kg Intraperitoneal LD_{50} (mus): 3.6 g/kg Subcutaneous LD_{50} (mus): 2.65 g/kg Skin irritant (rbt): 10 mg, 24 hr Eye irritant (rbt): 5 mg, severe
Reference Source(s):	Hoy, 1970; RTECS, 1980; Sax, 1979

Simulant:	Di(2-ethylhexyl)ether	2-Undecanol
Formula:	$C_{16}H_{34}O$	$CH_3CH(CH_2)_8CH_3$ OH
CAS Reg. No.:	10143-60-9	1635-30-1
Molecular Weight:	242.5	172.31
Chemical State (20°C):		colorless liquid
Liquid Density (g/cc):		0.8363
Vapor Density (compared to air):		
Freezing/Melting Point (°C):		12°
Boiling Point (°C):	269.1°	228-229° (Sax, 1979) 235.9° (Hoy, 1970)
Flash Point (°C):		113°
Vapor Pressure (mm Hg at 20°C):	0.018	0.02 at 25°
Odor:		
Toxicity:	Oral LD_{50} (rat): 34g/kg Skin irritant (rbt): 10 mg, 24 hr - mild Eye irritant (rbt): 500 mg	Oral LD_{50} (rat): 3 g/kg Dermal LD_{50} (4.76 g/kg Deemed to be G, maximum level of 20 ppm in baked goods
Reference Source(s):	Hoy, 1970; Lyman et al., 1982; RTECS, 1980	Food Chemical News Guide, 1982; Hoy, 1970; Sax, 1979

Simulant:	Dypnone	2-Hydroxyethyl-n-octyl sulfide
Formula:		$C_{10}H_{22}OS$
CAS Reg. No.:	1322-90-3	3547-33-9
Molecular Weight:	222.27	190.38
Chemical State (20°C):	liquid	
Liquid Density (g/cc):	d_{20}^{20} 1.093	
Vapor Density (compared to air):	7.67	
Freezing/Melting Point (°C):	-30°	
Boiling Point (°C):	340°-345° (partial decomp.)	257° (Lyman et al., 1982; Chapter 12, Meissner's method)
Flash Point (°C):	177° (open cup)	
Vapor Pressure (mm Hg at 20°C):	0.00037	0.0026 (Lyman et al., 1982; Chapter 22, method 1)
Odor:	Fruity	
Toxicity:	Oral LD_{50} (rat): 3.6 g/kg	Oral LD_{50} (rat): 8.53 g/kg Dermal LD_{50} (rbt): 13.59 g/kg
Reference Source(s):	Lyman et al., 1982; RTECS, 1980; Sax, 1979; Stecher, 1968	Lyman et al., 1982; RTECS, 1980

NONVOLATILE

Simulant:	2-(o-Hydroxyphenyl)-benz-oxazole	Tetraethylene Glycol
Formula:	$C_{13}H_9NO_2$	$C_8H_{18}O_5$
CAS Reg. No.:	835-64-3	112-60-7
Molecular Weight:	211.23	194.26
Chemical State (20°C):		colorless to pale straw-colored liquid
Liquid Density (g/cc):		d_4^{15} 1.1285
Vapor Density (compared to air):		
Freezing/Melting Point (°C):	121°-124°	-6.2°
Boiling Point (°C):	338°	328°
Flash Point (°C):		182° (open cup)
Vapor Pressure (mm Hg at 20°C):	2.3×10^{-8} (Lyman et al., 1982)	7.8×10^{-6} (Lyman et al., 1982)
Odor:		
Toxicity:	Intraperitoneal LD_{50} (mus): 2 g/kg	Oral LD_{50} (rat): 29 g/kg Skin irritant (rbt): 550 mg, unoccluded - mild Eye irritant (rbt): 565 mg Intravenous toxicity in anesthetized rats not dependent on rate of infusion up to 22 ml/hr. Higher infusion rates increased toxicity (Weifenbach, 1973)
Reference Source(s):	Aldrich, 1980; Lyman et al., 1982; RTECS, 1980	Aldrich, 1980; Lyman et al., 1982; RTECS, 1980; Sax, 1979; Weifenbach, 1973

APPENDIX B

DISQUALIFIED CANDIDATE SIMULANTS

Reason(s) for Disqualification

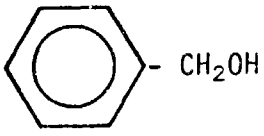
A Pharmacokinetics/metabolic pathway data required

B Possible difficulty in differentiating the compound and/or its metabolites in biological fluids from background

C Compound might require derivatization prior to analysis in urine

D Spot test not readily available

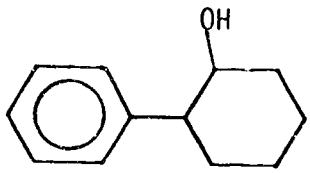
LOW

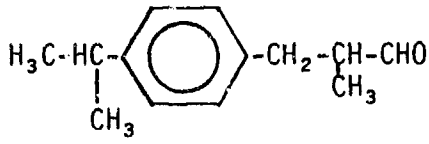
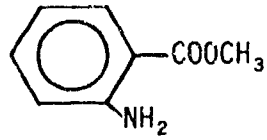
Simulant:	4-Methoxybenzyl Alcohol	n-Pentadecane
Formula:		$CH_3(CH_2)_{13}CH_3$
CAS Reg. No.:	105-13-5	629-62-9
Molecular Weight:	138.17	212.42
Chemical State (20°C):	liquid	
Liquid Density (g/cc):	1.108	0.769
Vapor Density (compared to air):		
Freezing/Melting Point (°C):	24°	9.9°
Boiling Point (°C):	259°	270.6°
Flash Point (°C):	>112°	132°
Vapor Pressure (mm Hg at 20°C):	3.8×10^{-3} (est.)	1.0×10^{-2} (est.)
Odor:		
Toxicity:	p.o. rat 1.2 g/kg p.o. mus 1.6 g/kg	i.v. mus 3.5 g/kg
Reference Source(s):	Aldrich, 1980; RTECS, 1980; Sax, 1979.	Aldrich, 1980; Clayton and Clayton, 1981; RTECS, 1980.
Reason(s) for Disqualifications:	A	D

LOW

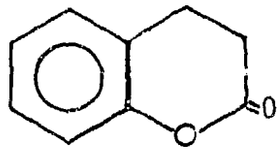
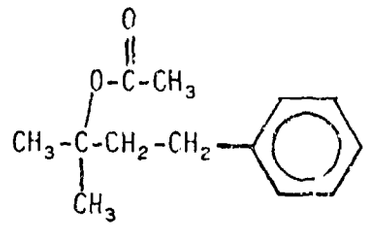
Simulant:	p-Methoxyacetophenone	1,4-Cyclohexanedi-methanol
Formula:		$C_6H_{10}(CH_2OH)_2$
CAS Reg. No.:	100-06-1	105-08-8
Molecular Weight:	150.18	144.21
Chemical State (20°C):		
Liquid Density (g/cc):		
Vapor Density (compared to air):		
Freezing/Melting Point (°C):	36°	
Boiling Point (°C):	bp 26 mm 152°	283°
Flash Point (°C):		161°
Vapor Pressure (mm Hg at 20°C):	3.3×10^{-3} (est.)	1×10^{-3} (est.)
Odor:		
Toxicity:	p.o. rat 1.72 g/kg	p.o. rat LDLo 3.2 g/kg i.p. rat LDLo 0.8 g/kg
Reference Source(s):	Aldrich, 1980; RTECS, 1980	Aldrich, 1980; RTECS, 1980
Reason(s) for Disqualifications:	A	A

LOW

Simulant:	N-n-Butyldiethanolamine	2-Phenyl-1-cyclo-hexanol
Formula:	$CH_3(CH_2)_3N(CH_2CH_2OH)_2$	
CAS Reg. No.:	102-79-4	1444-64-0
Molecular Weight:	161.25	176.28
Chemical State (20°C):		Colorless to pale yellow liquid
Liquid Density (g/cc):	0.968	d_{25}^{25} 1.033
Vapor Density (compared to air):	5.55	6.13
Freezing/Melting Point (°C):	-70°	
Boiling Point (°C):	bp 741 mm 273°	276°-281°
Flash Point (°C):	126°	>112°
Vapor Pressure (mm Hg at 20°C):	4.3×10^{-4} (est.)	1.4×10^{-3} (est.)
Odor:		
Toxicity:	p.o. rat 4.25 g/kg	p.o. rat 3.5 g/kg p.o. gpg 1.6 g/kg
Reference Source(s):	RTECS, 1980; Sax, 1979; Aldrich, 1980	RTECS, 1980; Aldrich, 1980; Sax, 1979
Reason(s) for Disqualifications:	A	A

Simulant:	2-Methyl-3-(p-isopropyl-phenyl)-priopionaldehyde	Methyl-2-aminobenzoate
Formula:		
CAS Reg. No.:		134-20-3
Molecular Weight:	190.28	151.17
Chemical State (20°C):	colorless to pale yellow liquid	colorless to pale yellow liquid
Liquid Density (g/cc):		1.163
Vapor Density (compared to air):		
Freezing/Melting Point (°C):		24°
Boiling Point (°C):	270°	256°
Flash Point (°C):		
Vapor Pressure (mm Hg at 20°C):	1.3×10^{-2} (est.)	6.9×10^{-3} (est.)
Odor:	sweet, flowery	grape-like
Toxicity:	p.o. rat 3.8 g/kg	p.o. rat 2.9 g/kg p.o. mus 3.9 g/kg
Reference Source(s):	RTECS, 1980; Furia and Bellanca, 1975	RTECS, 1980; Chemalog, 1981
Reason(s) for Disqualifications:	A	A, B

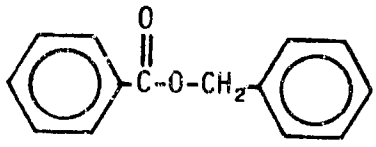
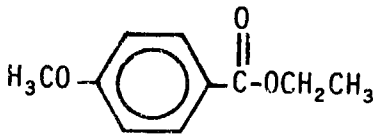
LOW

Simulant:	Dihydrocoumarin	2-Methyl-4-phenyl-2-butyl acetate
Formula:		
CAS Reg. No.:	119-84-6	
Molecular Weight:	148.16	206.28
Chemical State (20°C):		liquid
Liquid Density (g/cc):	1.169	
Vapor Density (compared to air):		
Freezing/Melting Point (°C):	25°	
Boiling Point (°C):	272°	275°
Flash Point (°C):		101°
Vapor Pressure (mm Hg at 20°C):	2.8×10^{-3} (est.)	1.4×10^{-2} (est.)
Odor:		jasmine
Toxicity:	p.o. rat 1.46 g/kg i.p. mus 0.2 g/kg	p.o. rat 4.85 g/kg
Reference Source(s):	RTECS, 1980; Chemalog, 1981	RTECS, 1980; Furia and Bellanca, 1975
Reason(s) for Disqualifications:	A	A

Simulant:	2,2'-Thiodiethanol	Tributyl Phosphite
Formula:	$(CH_2CH_2OH)_2S$	$(C_4H_9)_3PO_3$
CAS Reg. No.:	111-48-8	102-85-2
Molecular Weight:	122.2	250.36
Chemical State (20°C):	colorless liquid	liquid
Liquid Density (g/cc):	1.184	0.9
Vapor Density (compared to air):	4.21	
Freezing/Melting Point (°C):	-11°	
Boiling Point (°C):	282°	bp 7 mm 120°
Flash Point (°C):	160° (open cup)	120° (open cup)
Vapor Pressure (mm Hg at 20°C):	6.1×10^{-4} (est.)	1.6×10^{-2} (est.)
Odor:		
Toxicity:	p.o. gpg 3.96 g/kg i.v. rbt 3 g/kg	p.o. rat 3 g/kg
Refererce Source(s):	RTECS, 1980; Stecher, 1968; Aldrich, 1980; Sax, 1979	Aldrich, 1980; Stecher, 1968; RTECS, 1980
Reason(s) for Disqualifications:	A	A, B, D

Simulant:	1-Tridecanol	Triethylene Glycol
Formula:	$C_{12}H_{25}CH_2OH$	$(CH_2OCH_2CH_2OH)_2$
CAS Reg. No.:	112-70-9	112-27-6
Molecular Weight:	200.4	150.17
Chemical State (20°C):	water-white liquid	colorless liquid
Liquid Density (g/cc):	0.845	d_{25}^{25} 1.122
Vapor Density (compared to air):	6.9	5.17
Freezing/Melting Point (°C):		-7.3°
Boiling Point (°C):	bp 15 mm 115°	285-291°
Flash Point (°C):	121° (open cup)	166° (open cup)
Vapor Pressure (mm Hg at 20°C):	1.3×10^{-3} (est.)	2.4×10^{-3} (est.)
Odor:	pleasant	odorless
Toxicity:	p.o. rat LDLo 4.75 g/kg derm rbt 7.1 g/kg	p.o. rat 17 g
Reference Source(s):	Sax, 1979; Aldrich, 1980; RTECS, 1980	Aldrich, 1980; Sax, 1979; Marsden and Mann, 1963
Reason(s) for Disqualifications:	A	A

LOW

Simulant:	Benzyl Benzoate	Ethyl-p-anisate
Formula:		
CAS Reg. No.:	120-51-4	94-30-4
Molecular Weight:	212.24	180.21
Chemical State (20°C):	colorless, oily liquid	liquid
Liquid Density (g/cc):	1.114	
Vapor Density (compared to air):	7.3	
Freezing/Melting Point (°C):	18-21°	7-8°
Boiling Point (°C):	324°	263°
Flash Point (°C):	148°	263°
Vapor Pressure (mm Hg at 20°C):	9.5×10^{-4} (est)	2.0×10^{-2}
Odor:	light, balsamic odor reminiscent of almonds	sweet fruity, anise-like
Toxicity:	p.o. rat 1.7 g/kg p.o. gpg 1 g/kg derm rat 4 g/kg	p.o. rat 2.04 g/kg
Reference Source(s):	Furia and Bellanca, 1975; Kirk-Othmer, 1978; Sax, 1979; Stecher, 1968	RTECS, 1980; Furia and Bellanca, 1975
Reason(s) for Disqualifications:	A	A

LOW

Simulant:	α-Santalol
Formula:	$C_{15}H_{24}O$
CAS Reg. No.:	115-71-9
Molecular Weight:	220.34
Chemical State (20°C):	colorless to pale yellow liquid
Liquid Density (g/cc):	d_{25}^{25} 0.965-0.98
Vapor Density (compared to air):	
Freezing/Melting Point (°C):	
Boiling Point (°C):	302°
Flash Point (°C):	
Vapor Pressure (mm Hg at 20°C):	2.4×10^{-4} (est)
Odor:	sweet, sandalwood
Toxicity:	p.o. rat 3.8 g/kg
Reference Source(s):	RTECS, 1980; Furia and Bellanca, 1975; Stecher, 1968
Reason(s) for Disqualifications:	A

APPENDIX C

UNACCEPTABLE CANDIDATES EXAMINED

Reason(s) for Elimination

A Carcinogen/suspect carcinogen

B Chronic toxic effects

C Mutagen

D Suspect teratogen

E Emits toxic fumes

F Oral LD_{50} too low

G Dermal LD_{50} too low

H Acute parental LD_{50} values too low

I Neurotoxic

J Potent photoallergen

K No toxicity information found in standard reference sources

L Solid at 20°C

M Detection problems

N Spot test not readily available

O Extensively metabolized/detection obscured by high background values

APPENDIX C

UNACCEPTABLE CANDIDATES EXAMINED

Chemical	CAS Reg. No.	Reason(s) for Elimination
LOW GROUP		
butyl digol		B
cinnamonitrile	1885-38-7	A
butyl carbitol	112-34-5	B
phenethyl tiglate	55719-85-2	G
γ-undecalactone	104-67-6	A,M,N
10-undecen-1-yl-acetate	112-19-6	G,N
linayl cinnamate		A
cinnamyl butyrate	103-61-7	A
cinnamyl isovalerate		A
cinnamyl phenylacetate		A
tetramethylene sulfone	126-33-0	F,M,N
methyl cinnamaldehyde	101-39-3	A
NON-VOLATILE GROUP		
2-aminobiphenyl	90-41-5	A
6-methyl coumarin	92-48-8	C,J,L
BOILING POINT >250° GROUP		
butyl anthranilate		F
N-butylacetanilide		F
dibutyl sebacate		K
decanoic acid		H
dihydrocoumarin		H,L
2,6-dimethyl-10-methylene -2,6,11-dodecatrienal		K
γ-dodecalactone		K
(+)-diethyl L-tartrate		K
3,4-dimethoxybenzaldehyde		L

APPENDIX C

UNACCEPTABLE CANDIDATES EXAMINED (cont'd.)

Chemical	CAS Reg. No.	Reason(s) for Elimination
3,4-dimethoxy benzyl alcohol		K
1,2-dimethoxy-4-propenyl benzene		H
2,4-dimethyl benzoic acid		K
2,5-dimethyl benzoic acid		K
dimethyl suberate		K
2,4-dimethyl sulfolane		F,G
1,3-dimethylurea		D,L
di-n-octyl amine		H
diphenyl acetaldehyde		H
diphenylamine		A,D,E
1,4-diphenyl-1,3-butadiene		K
diphenyl-1,3-butadiene		K
diphenyl carbonate		A,L
1,1-diphenylethylene		K
1,2-diphenylethylamine		K
2-dodecanal		K
2,2'-diphenol		K
2,4-diisopropyl phenol		K
o-ethoxybenzyl alcohol		K
p-ethoxybenzyl alcohol		K
ethyl 2-acetyl-3-phenyl propionate		K
ethyl-2-benzyl-benzoylacetate		K
ethyl benzoylacetate		K
α-ethyl benzyl butyrate		K
ethyl laurate		K
ethyl undecanoate		K
ethyl-10-undecenoate		K
eugenol		H
3-ethoxy salicylaldehyde		K
2-hydroxy-5-methoxybenzaldehyde		H
4-hydroxy-3-methyl-2-butanone		K

APPENDIX C

UNACCEPTABLE CANDIDATES EXAMINED (cont'd.)

Chemical	CAS Reg. No.	Reason(s) for Elimination
n-heptadecanoic acid		H
n-heptadecane		K
n-hexadecane		H,I
1-hexadecanol		L
1-hexadecane		K
isoamyl nonylate		K
isoamyl phenylacetate		K
isoamyl salicylate		H
isobutyl phenylacetate		K
isopropyl acetophenone		K
isopropyl phenylacetate		K
lipidine		K
isopropyl laurate		K
isopropyl caprate		K
linayl octanoate		K
3-methoxy benzyl alcohol		K
methyl palmitate		K
methyl laurate		K
methyl dihydrojasmonate		K
methyl myristate		K
4-methyl-1-phenyl-2-pentanone		K
methyl undecyl ketone		L
nonyl isovalerate		K
nonyl octanoate		K
octyl octanoate		K
phenylethyl hexanoate		K
phenylethyl isovalerate		K
phenethyl octanoate		K
2-phenoxyethyl isobutyrate		K
1-phenyl-3-methyl-3-pentanol		K
3-phenyl propyl hexanoate		K

APPENDIX C

UNACCEPTABLE CANDIDATES EXAMINED (cont'd.)

Chemical	CAS Reg. No.	Reason(s) for Elimination
3-phenyl propyl isovalerate		K
3-phenyl propyl propionate		K
3-propylidene phthalide		K
rhodinyl isobutyrate		K
rhodinyl isovalerate		K
rhodinyl phenylacetate		K
rhodinyl propionate		K
propyl laurate		K
propyl caprate		K
1-octadecanol		L
octadecane		K
nonadecane		K
1,2-octanediol		K
methyl caprate		K
p-methoxybenzene thiol		H
4-(p-methoxy phenyl)-1-butanol		K
3-(o-methoxy phenyl)-1-butanol		K
3-(o-methoxy phenyl) propanol		K
6-methoxy-1-tetralone		L
3-methyl adipic acid		K
3-methyl diphenylamine		K
3-methyl indole		L
4-methyl-3-nitroanisole		K
methyl-m-nitrobenzoate		K
1-methyl-2-tetralone		K
2-methyl-1-tetralone		K
4-methyl-1-tetralone		K
methyl-3,4,5-trimethoxybenzoate		K
methyl vanillate		H
o-nitroanisole		K
o-nitrobenzyl alconol		K

APPENDIX C

UNACCEPTABLE CANDIDATES EXAMINED (cont'd.)

Chemical	CAS Reg. No.	Reason(s) for Elimination
nonanoic acid		H
n-pentadecanoic acid		H
phenylacetic acid		E,L
phenyl benzoate		L
1-phenyl decane		K
m-phenylenediamine		F,L
phenyl ether		L
phenyl salicylate		L
phenyl sulfoxide		H
pimelic acid		L
piperonal		L
suberic acid		L
terpinyl cinnamate		A,K
tetrahydrofurfuryl cinnamate		A,K
triethanolamine		A
tributyl acetyl citrate		K
triethyl thiophosphate		H
tri-n-octylamine		H
triphenylamine		L
triphenylene		L
triphenylmethanol		L
triphenyl phosphate		H,L
tris(hydroxymethyl)amino methane		L
undecanoic acid		H
undecylenic acid		H
ω-undecylenyl alcohol		K

BIBLIOGRAPHY

Anonymous, 1979, Household insecticides: Which are worse, bugs or bug killers? Consumer Reports 44:362-367.

Anonymous, 1981 Individual susceptibility. Lancet 1:368.

Ambrose, A.M.; Huffman, D.K.; Salamone, R.T., 1958, Comparative studies on toxicity of ortho, meta and para isomers of N,N-diethyltoluamide. Fed. Proc. 17. Abstract.

Ambrose, A.M.; Yost, D.H., 1965, Pharmacologic and toxicologic studies of N,N-diethyltoluamide. II. N,N-diethyl-o-toluamide and N,N-diethyl-p-toluamide. Toxicol. Appl. Pharmacol. 7:772-780.

American Conference of Governmental Industrial Hygienists (ACGIH), 1980, Documentation of the Threshold Limit Values, 4th ed. Cincinnati, Ohio.

American Conference of Governmental Industrial Hygienists (ACGIH), 1981, TLVs Threshold Limit Values for Chemical Substances and Physical Agents in the Workroom Environment with Intended Changes for 1981. Cincinnati, Ohio.

Arena, J.M., 1979, Poisoning. Toxicology. Symptoms. Treatments. 4th ed. Springfield, Illinois:Charles C. Thomas Publ..

Ariyoshi, T.; Tachikawa, R.; Minami, M.; Noda, K., Inoue, H., 1979, Studies on d-limonene as a gallstone solubilizer. Oyo Yakuri 18:195-201. Abstract.

Ashcroft, R.G.; Coster, H.G.L.; Smith, J.R., 1977, Local anesthetic benzyl alcohol increases membrane thickness. Nature 269:819-820.

Boublík, T.; Fried, V.; Hála, E., 1973, The Vapor Pressures of Pure Substances. Amsterdam:Elsevier Scientific Publishing Co..

Bourg, R.; van Meensel, F., 1956, Action of some oily solvents of hormonal preparations on the testicle, the genital tract, and the mammary glands of the male adult rat. Annee Endocrinol. 17:250-260. Abstract.

Browning, E., 1953, Toxicity of Industrial Organic Solvents. New York: Chemical Publishing Co..

Clayton, P.; Martin, K., 1971, The effect of anaesthetic alcohols on carrier mediated transport in human erythrocytes. J. Physiol. 218:50p-51p.

Collins, T.F.X.; Hansen, W.H.; Keeler, H.V., 1969, The effect of methyl salicylate on rat reproduction. Toxicol. Appl. Pharmacol. 14:653. Abstract.

Doull, J.; Plzak, V.; Brois, S.J., 1962, A survey of compounds for radiation protection. School of Aerospace Medicine, USAF Aerospace Medical Division, Brooks AFB, TX. NTIS Report No. AD277-689, 124p.

Dremova, V.P.; Gleyberman, S.E.; Smirnova, S.N.; Voronkina, T.V.; Tsetlin, V.M.; Markina, V.V., 1974, DETA-1 lotion: Its repellent effectiveness and toxicity to warm-blooded animals. Med. Parazitol. Parazit. Bolezni 43:67-73. Abstract.

Duncan, D.; Jarvis, W., 1941, Effects on the facial nerve of component substances used in certain anesthetic mixtures dissolved in oil. Proc. Trans. Texas Acad. Sci. 25:54-55. Abstract.

Ehrlich, K.C.; Klein, E.; Smith, J.K., 1977, Development of an on-line biological detector. Order No. AD-A067584:47 pp.

Erickson, M.D.; Harris, B.S.H., III; Pellizzaro, E.D.; Tomer, K.B.; Waddell, R.D., 1980, Acquisition and chemical analysis of mother's milk for selected toxic substances. EPA Report 560/13-80/029, PB81-231029, 164pp. Abstract.

Falk, M.S., 1976, Contact urticaria syndrome. Arch. Dermatol. 112:559 (letter).

Federal Register, 1978, Proposed regulations for control of organic chemical contaminants in drinking water. Vol. 43:29135-29150.

Gaulejac, R. de; Dervillée, P., 1938, Sur quelques cas d'intoxication par les vapeurs de benzène et d'alcool benzylique. [Some cases of intoxication with benzene and benzyl alcohol vapors.] Ann. Med. Leg. 18:146-152.

Gleiberman, S.E.; Volkova, A.P., 1971, Toxicological comparison of diethyltoluamides as synthesized from petroleum and coal metaxylen. Med. Parazitol. 40:39-45. Abstract.

Gleiberman, S.E.; Voronkina, T.M.; Latyshev, V.I.; Tsetlin, V.M.,1974, Resorptive excretory properties of some repellents. Med. Parazitol. Parazit. Bolezni 43:446-455. Abstract.

Gmehling, J.; Onken, V.; Arlt, W., 1980-1982, Vapor-Liquid Equilibrium Data Collection. Vol. 1 of Chemistry Data Series. Frankfurt (W. Ger.):DECHEMA: parts 1-7.

Gordon, L.M.; Sauerheber, R.D.; Esgate, J.A.; Dipple, I.; Marchmont, R.J.; Houslay, M.D., 1980, The increase in bilayer fluidity of rat liver plasma membranes achieved by the local anesthetic benzyl alcohol affects the activity of intrinsic membrane enzymes. J. Biol. Chem. 255(10):4519-4527.

Graham, B.E.; Kuizenga, H.H., 1945, Toxicity studies on benzyl benzoate, and related benzyl compounds. J. Pharmacol. 84:358-362. Abstract.

Grant, W. M., 1962, Toxicology of the Eye. Springfield, Illinois:Charles C. Thomas Publisher.

Gross, M.; Fitzhugh, O.; Mantel, N., 1970, Evaluation of safety for food additives: An illustration involving the influence of methyl salicylate on rat reproduction. Biometrics 26:181-194.

Gruber, C.M.; Shackelford, H.H., 1924, The pharmacology of benzyl alcohol and its esters. III. Some observations on the effect of benzyl-benzoate upon arterial hypertension in man. J. Lab. Clin. Med. 9:685-698.

Hanai, T.; Hubert, J., 1982, Hydrophobicity and chromatographic behaviour of aromatic acids found in urine. J. Chromatogr. 239:527-536.

Hill, J.A.; Robinson, P.B.; McVey, D.L.; Akers, W.A.; Reifenrath, W.G., 1979, Evaluation of mosquito repellents on the hairless dog. Mosq. News 39(2):307-310.

Hirschfelder, A.D., 1920, Recent studies upon the therapeutic application of benzyl alcohol, benzyl benzoate and some homologous compounds. Minn. Med. 3:380-382.

Holmberg, B.; Malmfors, T., 1974, Cytotoxicity of some organic solvents. Environ. Res. 7(2):183-192.

Huang, H.; Wang, C.; Lin, T.; Junior, C.T.; Jen, H.W., 1978, A simple quantitative determination of essential oils in external dermatics. T'ai-wan Yao Hsueh Tsa Chih 30:107. Abstract.

Imaseki, I.; Kitabatake, Y., 1962, Effect of essential oils and their components on the isolated intestine of mice. Yakugaku Zasshi 82:1326-1328. Abstract.

Jordan, T.E., 1954, Vapor Pressure of Organic Compounds. New York:Interscience Publishers.

Karasek, F.W.; Kim, S.H., 1974, The plasma chromatograph as a qualitative detector for gas chromatography. J. Chromatogr. 99:257-266.

Kellner, W.; Kober, W., 1955, Moglichkeiten der verwendung atherischer ole zur raumdesin fektion. [The possibility of using ethereal oils for the disinfection of rooms.] Arzneim. -Forsch. 5:224-229.

King, B.M.; Solms, J , 1979, Interactions of flavor compounds in model food systems using benzyl alcohol as an example. J. Agric. Food Chem. 27:1331-1334.

Kitagawa, H.; Saito, H.; Mori, M.; Tazoe, R., 1979a, Anti-inflammatory and analgesic action of salicylate plaster. Oyo Yakuri 18:647-651. Abstract.

Kladnig, W.F.; Weiss, A.H.; Jonas, L.A., 1979, A test for residual adsorption capacity of charcoal filters. Ext. Abstr. Program - Bicenn. Conf. Carbon 14:24-25.

Kligman, A.M., 1975, Report to RIFM, 17 June. (As cited by Opdyke, 1978d).

Komarova, E.N., 1979, Materials on the toxicology of dibutyl phthalate, dioctyl phthalate, dibutyl sebacate and butyl stearate. Khim. Prom.-st. ser.:Toksikol. Sanit. Khim. Plastmass 3:12-15. (As cited in CA/093/038845N).

Konovalov, G.A.; Romanov, A.N., 1980, Early hemodialysis in the treatment of intoxication caused by the repellents N,N-diethyl-m-toluamide, benphthalate, dimethylphthalate. Anesteziol. Reanimatol. 2:54-55. Abstract.

Kucera, J., 1963, Chromatography of some aliphatic alcohols, glycols and diketones on a thin layer of alumina. Collect. Czech. Chem. Commun. 28:1341-1344.

Kuchukhidze, G.E.; Dolidze, T.G., 1975, Effect of cyclohexanone, caprolactam, and dinil on the reproductive function of workers in industry. Sb. Tr., Nauchno-Issled. Inst. Gig. Tr. Profzabol., Tiflis 14:188-198. Abstract.

Labat, C.; Oustrin, J., 1979, Study of a natural mixture of terpenes. Identification of constituents. Absorption and fate in the rat after intramuscular injection. Ann. Pharm. Fr. 37:377-384. Abstract.

Labows, J.; Preti, G.; Hoelzle, E.; Leyden, J.; Kligman, A., 1979, Analysis of human axillary volatiles: compounds of exogenous origin. J. Chromatogr. 163:294-299.

Lacko, L. Wittke, B.; Lacko, I., 1978, Inhibition of glucose transport in human erythrocytes by benzyl alcohol. J. Cell. Physiol. 96:199-201.

Lejhancová, G.; Wolf, J., 1955, Effect of terpenes and their oxidation products on the skin. Prac. Lék. 7:285-289. Abstract.

Macht, D.I., 1919, Further experiences with benzyl benzoate and benzyl alcohol. J. Pharm. Proc. 13:509. Abstract.

Macht, D.I., 1920, Benzyl alcohol for toothache. J.A.M.A. 75:1205.

Macht, D.I.; Leach, H.P., 1929, Concerning the antipyretic properties of benzyl benzoate. J. Pharmacol. Exper. Therap. 35:281-296. Abstract.

Masherpa, P , 1937, The excretion of limonene by rabbits. Boll. Soc. Med. -Chir. Catania 5:398-408. Abstract.

Menczel, E.; Maibach, H.I., 1970, In vitro human percutaneous penetration of benzyl alcohol and testosterone: epidermal-dermal retention. J. Invest. Dermatol. 54:386-394.

Metcalfe, S.M., 1971, Cell culture as a test system for toxicity. J. Pharm. Pharmac. 23:817-823.

Mikhailov, P.; Berova, N., 1970, Clinical and biochemical studies on turpentine contact allergy. Dermatol. Veenerol. 19:20-24. Abstract.

Mitzner, B.M.; Mancini, V.J.; Shiftan, T.A., 1966, Silicone treatment of the solid support in gas chromatography: its effect on retention times. J. Gas Chromatog. 4:336-337.

Nakano, M., 1958, Effect of various antifungal preparations on the conjunctiva and cornea of rabbits. Yakuzaigaku 18:94-99. Abstract.

Nelson, K.W.; Ege, J.F., Jr.; Ross, M.; Woodman, L.E.; Silverman, L., 1943, Sensory response to certain industrial solvent vapors. J. Ind. Hyg. and Tox. 25:282-285.

Northover, B.J.; Verghese, J., 1962, The pharmacology of certain terpene alcohols and oxides. J. Sci. Ind. Res. 21C:342-345.

Odom, R.B.; Maibach, H.I., 1977, Contact urticaria: A different contact dermatitis. Marzulli, F.N.; Maibach, H.I., eds. Advances in Modern Toxicology, Dermatotoxicology and Pharmacology. Washington, DC:Hemisphere Publishing Corp. 4:441-453.

Okamoto, N., 1969, Experimental production of congenital cardiovascular anomalies (Concluded). Congenital Anomalies 9(3):117-132. Abstract.

Perry, R.H.; Chilton, C.H., eds., 1973, Chemical Engineers' Handbook, 5th ed. New York:McGraw-Hill Book Co..

Pertsovskii, A.L.; Markovskaya, T.V., 1976, Gas-chromatographic determination of dibutyl sebacate in the air of industrial premises. Aktual. Vopr. Okhr. Tr. Khim. Prom.-sti:93-94. (As cited in CA/090/109007S).

Pienta, R.J., 1979, A hamster embryo cell model system for identifying carcinogens. Griffin, A.C.; Shaw, C.R., eds. Carcinogens: Identification and Mechanisms of Action. New York:Raven Press; pp121-141.

Pirila, V.; Kilpio, O.; Olkkonen, A.; Pirila, L.; Siltanen, E., 1969, On the chemical nature of eczematogens in oil of turpentine. V. Pattern of sensitivity to different terpenes. Dermatologica 139:183-194.

Pitini, A.; Fernandez, G., 1922, Pharmacological action of an oil (antisapros) extracted from the turpentines of Pinus pinea. Riv. Ital. Essenze Profumi 4:127-130. Abstract.

Radziemski, L.J., Jr., 1981, Laser-induced photodestruction of the organo-phosphates: DIMP and DMMP. J. Environ. Sci. Health B16(3):337-361.

Riedel, H., 1940, Effects of some terpenes on the skin. Klin. Wochschr. 19:1034-1036. (As cited in J. Ind. Hyg. Abs. 24:76; 1942).

Roe, F.J.C., 1960, Some newly discovered tumour-promoting substances. Abh. Dtsch. Akad. Wiss. Berlin, Kl. Med. 3:36-40.

Rosenkranz, H.S.; Leifer, Z., 1980, Determining the DNA-modifying activity of chemicals using DNA polymerase-deficient Escherichia coli. Chem. Mutagens:Prin. Methods Their Detection 6:109-147.

Roskam, R.Th., 1958, The preservation of shrimp. Conserva 6:278-281; 308-310. Abstract.

Rossi, A., 1947, Experiments on the elimination of limonene by respiration. Farm. Sci. e Tec. (Pavia) 2:107-111. Abstract.

Roth, G.B.; Kane, H.F., 1937, The effect of paraldehyde and benzyl alcohol on uterine activity. J. Lab. Clin. Med. 22:477-484.

Scherr, G.H.; Severens, J.M.; Jurtshuk, P., Jr.; Wittenberger, C.L., 1954, Effect of cortisone (adrenocortical preparation) and somatotropic hormone on vaccinia virus lesions and benzyl alcohol toxicity in embryonated egg. J. Infect. Dis. 95:160-164.

Skinner, W.A.; Tong, H.C.; Johnson, H.; Parkhurst, R.M.; Thomas, D.; Spencer, T.; Akers, W.; Skidmore, D.; Maibach, H., 1977, Influence of human skin surface lipids on protection time of topical mosquito repellent. J. Pharm. Sci. 66:1764-1766.

Smith, S.C.; Monie, I.W., 1969, Normal and abnormal nasolabial morphogenesis in the rat. Teratology 2:1-12.

Smyth, H.F., Jr.; Carpenter, C.P.; Weil, C.S., 1951, Range-finding toxicity data. List IV. Arch. Ind. Hyg. Occup. Med. 4:119-122. Abstract.

Smyth, H.F., Jr.; Carpenter, C.P.; Weil, C.S.; Pozzani, U.C.; Striegal, J.A.; Nycum, J.S., 1969, Range-finding toxicity data: List VII. Am. Ind. Hyg. Assoc. J. 30:470-476.

Snapper, L.; Grunbaum, A.; Sturkop, S., 1925, Oxidation of benzyl alcohol and benzyl esters in the human organism. Biochem. Z. 155:163-173. Abstract.

Solan, J.L.; Laden, K., 1977, Factors affecting the penetration of light through stratum corneum. J. Soc. Cosmet. Chem. 28:125-137.

Sollmann, T., 1919, The anesthetic efficiency of benzyl alcohol for mucous membranes. J. Pharmacol. 13:355-360. Abstract.

Suzuki, Y.; Ito, M.; Sano, J., 1980, Studies on anti-inflammatory and analgesic actions of cataplasmas. Oyo Yakuri 19:239-246. Abstract.

Szabo, K.T.; Kang, J.Y., 1969, Comparative teratogenic studies with various therapeutic agents in mice and rabbits. Teratology 2:270. Abstract.

Teuchy, H.; Quatacker, J.; Wolf, G.; Van Sumere, C.F., 1971, Quantitative investigation of the hippuric acid formation in the rat after administration of some possible aromatic and hydroaromatic precursors. Arch. Int. Physiol. Biochim. 79:573-587.

Tolleshaug, H.; Berg, T., 1982, Evidence for the selective inhibition of fusion between endocytic vesicles and lysosomes by benzyl alcohol. Biochem. Pharmacol. 31(4):593-595.

Treon, J.F.; Crutchfield, W.E., Jr.; Kitzmiller, K.V., 1943a, The physiological response of rabbits to cyclohexanone, methylcyclohexanone and certain derivatives of these compounds. I. Oral administration and cutaneous application. J. Ind. Hyg. Toxicol. 25:199-214.

Treon, J.F.; Crutchfield, W.E., Jr.; Kitzmiller, K.V., 1943b, The physiological response of rabbits to cyclohexanone, methyl cyclohexanone and certain derivatives of these compounds. II. Inhalation. J. Ind. Hyg. Toxicol. 25:323-347.

Uges, D.R.A.; Bloemhof, H.; Christensen, E.K.J., 1981, An HPLC method for the determination of salicylic acid, phenacetin and paracetamol in serum, with indications; two case-reports of intoxication. Pharm. Weekbl., Sci. Ed. 3(5):1309-1315.

Valette, G.; Cavler, R., 1954, Absorption percutanée et constitution chimique. Cas des hydrocarbures, des alcools et des esters. [Percutaneous absorption and chemical constitution. Hydrocarbons, alcohols and esters.] Arch. Intern. Pharmacodynamie 97:232-240.

Vashkov, V.I.; Gleiberman, S.E.; Volkova, A.P., 1976, Study of the remote consequences of the use of repellents. Part II. Some problems regarding regulation of the use of the repellent diethyl toluamide (DEET). Med. Parazitol. Bolezni 45:720-725. Abstract.

Verghese, J., 1969, The chemistry of limonene and of its derivatives: Part IV. Perfum. Essent. Oil Rec. 60:271-276.

Warkany, J.; Takacs, E., 1959, Experimental production of congenital malformations in rats by salicylate poisoning. Am. J. Pathol. 35:315-331.

Weast, R.C.; Astle, M.J., eds., 1980, Handbook of Chemistry and Physics, 61st ed. Florida:CRC Press, Inc..

Weinberg, E.H.; Springer, S.T., 1981, The evaluation in vitro of fragrance materials for phototoxic activity. J. Soc. Cosmet. Chem. 32:303-315.

Weiss, G., ed., 1980, Hazardous Chemicals Data Book New Jersey:Noyes Data Corporation.

Wong, M.H.; Yew, D.T., 1978, Dermotoxicity of the mosquito repellent related to rabbit ears. Acta Anat. 100:129-131.

Yaws, C.L., 1977, Physical Properties - A Guide to the Physical, Thermodynamic and Transport Property Data of Industrially Important Chemical Compounds. New York:McGraw-Hill Book Co.

Yeager, J.F.; Wilson, C.S.,1944, New itch remedy. J. Lab Clin. Med. 29:177-178.

Zwolinski, B.J.; Wilhoit, R.C., 1971, Handbook of Vapor Pressures and Heats of Vaporization of Hydrocarbons and Related Compounds. Thermodynamic Research Center and American Petroleum Institute Research Report Project 44, College Station, Texas.

REFERENCES

Adams, J.T.; Bigler, J.A.; Green, O.C., 1957, A case of methyl salicylate intoxication treated by exchange transfusion. J. Am. Med. Assoc. 165:1563-1565.

Aldrich Catalog Handbook of Fine Chemicals, 1981-1982., 1980, Milwaukee, Wisconsin: Aldrich Chemical Co., Inc..

Ambrose, A.M., 1959, Pharmacologic and toxicologic studies on N,N-diethyltoluamide. I. N,N-diethyl-m-toluamides. Toxicol. Appl. Pharmacol. 1:97-115.

Angerhofer, R.A.,; Weeks, M.H., 1981, Phase 7: Effect of dermal applications of N,N-diethyl-meta-toluamide (m-Det) on the embryonic development of rabbits. USAEHA-75-51-0034-7 Order No. AD-A09477B; 22pp.

Atkinson, J.P.; Udey, M.C.; Wedner, H.J.; Parker, C.W., 1976, Studies on the stimulation of cAMP metabolism by heparin solutions containing benzyl alcohol. J. Cyclic Nucleotid Res. 2:297-305.

Bagramyan, S.B.; Babaian, E.A., 1974, [Cytogenetic study of the mutagenic action of chemical substances derived from nairit latexes MKH and LN-1.] Biol. Zh. Arm. 27(6):102-103. (As cited in NIOSH, 1978b).

Bagramyan, S.B.; Pogosian, A.S.; Babaian, E.A.; Ovanesian, R.D.; Charian, S.M., 1976, [The mutagenic action of low concentrations of volatile substances, emitted by polychloroprene latexes LNT-1 and MC, upon their joint entry into the organism.] Biol. Zh. Arm. 29:98-99. (As cited by NIOSH, 1978b; CA085/172283R).

Beatty, R.C.; Martin, K.J., 1978, Antagonistic effects of two anaesthetics of hypotonic haemolysis. Br. J. Pharmacol. 62:426P.

Berlin, A.R.; Miller, O.F., 1976, Allergic contact dermatitis from ethyl sebacate in haloprogin cream. Archives of Dermatology 112:1563-1564. (As cited by Schneider, 1980).

Bertone, L.L.; Monie, I.W., 1965, Teratogenic effect of methyl salicylate and hypoxia in combination. Anat. Rec. 151:443. Abstract.

Blau, S.; Kanof, N. Report to RIFM; 11 May, 1971. (As cited by Opdyke, 1975).

Blomquist, L.; Stroman, L.; Thorsell, W., 1975, Distribution and fate of the insect repellent ^{14}C-N,N-diethyl-m-toluamide in the animal body. I. Distribution and excretion after injection into mice. Acta Pharmacol. et Toxicol. 37:121-133.

Blomquist, L.; Thorsell, W., 1977, Distribution and fate of the insect repellent ^{14}C-N,N-diethyl-m-toluamide in the animal body. II. Distribution and excretion after cutaneous application. Acta Pharmacol. et Toxicol. 41:235-243.

Bowen, D.; Cowburn, D.; Rennekamp, M.; Sullivan, J., 1975, Benzyl alcohol: High levels found in plasma of uremic patients on hemodialysis. Clin. Chim. Acta 61:399-401.

Bray, H.G.; James, S.P.; Thorpe, W.V., 1958, Metabolism of some ω-halogenoalkylbenzenes and related alcohols in the rabbit. Biochem. J. 70:570-579.

Brooks, S.C.; Lalich, J.J.; Baumann, C.A., 1957, Skin sterols -- XII. Contrasting effects of certain mercaptans, amines, and related compounds on sterols and sebaceous glands. Cancer Res. 17:148-152.

Brown, W.J.; Buist, N.R.M.; Gipson, H.T.C.; Huston, R.K.; Kennaway, N.G., 1982, Fatal benzyl alcohol poisoning in a neonatal intensive care unit (letter). Lancet 1:1250.

Burg, A.; Ehntholt, D.; Ennis, J.; Smith, E., 1982, The development of a detection device for 1-butanethiol. Chemical Systems Laboratory Contractor Report ARCSL-CR-82025.

Cancelmo, J.J., 1948, A Methyl salicylate poisoning. J. Am. Med. Assoc. 136:651. Abstract.

Cann, H.M.; Verhulst, H.L., 1958, The salicylate problem with special reference to methyl salicylate. J. Pediatr. 53:271-276.

Center for Disease Control, 1982, Neonatal deaths associated with use of benzyl alcohol - United States. Morbidity and Mortality Weekly Report 31:290-291.

Chemalog Catalog/Handbook of Biochemicals and Organic Chemicals, 1981, Chemical Dynamics Corporation, South Plainfield, NJ 07080.

CHRIS, 1974, Hazardous Chemical Data, Report No. CG-446-2. Washington DC; Department of Transportation, U.S. Coast Guard.

Cirstea, M., 1972, Studies on the relation between chemical structure and contact sensitizing capacity of some thiol compounds. Rev. Roum. Physiol. 9:485-491. (As cited by NIOSH, 1978b).

Clayton, G.D.; Clayton, F.E. eds., 1981, Patty's Industrial Hygiene and Toxicology, 3rd revised ed., Vol. 2A, 2B, Toxicology. New York:John Wiley and Sons, Inc.

Collin, J.-P., 1971, Cytogenetic effect of cyclamate, cyclohexanone and cyclohexanol. Diabete 19:215-221.

Collins, T.F.X.; Hansen, W.H.; Keeler, H.V., 1971, Effect of methyl salicylate on rat reproduction. Toxicol. Appl. Pharmacol. 18:755-765.

Council of Europe, 1972, Natural and Artificial Flavouring Substances. Partial Agreement in the Social and Public Health Field, Strasbourg, Section VI, Series 1, No. 562:p68. (As cited by Opdyke, 1973).

Council of Europe, 1974, Natural and Artificial Flavouring Substances, Their Sources, and Added Artificial Flavouring Substances. Partial Agreement in the Social and Public Health Field, Strasbourg. List 1, Nos. 233, 234, 614, 623:pp.173, 254, 257. (As cited by Opdyke, 1975, 1978c,d and 1980).

Council of Europe, 1974, Natural and Artificial Flavouring Substances, Their Sources, and Added Artificial Flavouring Substances. Partial Agreement in the Social and Public Health Field, Strasbourg. List 2, No. 2150:314. (As cited by Opdyke, 1978e).

Davison, C.; Zimmerman, E.F.; Smith, P.K., 1961, On the metabolism and toxicity of methyl salicylate. J. Pharmacol. Exp. Ther. 132:207-211.

Dean, J.A., ed., 1979, Lange's Handbook of Chemistry, 12th ed. New York:McGraw-Hill Book Co.

Diack, S.L.; Lewis, H.B., 1928, Studies in the synthesis of hippuric acid in the animal organism. VII. A comparison of the rate of elimination of hippuric acid after the ingestion of sodium benzoate, benzyl alcohol and benzyl esters of succinic acid. J. Biol. Chem. 77:89-95.

Deichmann, W.B.; Gerarde, H.W., eds., 1969, Toxicology of Drugs and Chemicals. New York: Academic Press; pp394-395, 662.

Driedger, P.I.; Blumberg, P.M., 1978, Non-phorbol mouse skin tumor promoters do not mimic phorbol myristate acetate in its effects on chick embryo fibroblasts. Int. J. Cancer 22:63-69.

Duncan, D.; Jarvis, W.H., 1943, A comparison of the actions on nerve fibers of certain anesthetic mixtures and substances in oil. Anesthesiology 4:465-474.

Duraiswami, P.K., 1954, Experimental teratogenesis with benzyl alcohol; preliminary report. Bull. Johns Hopkins Hosp. 95:57-67.

Dyshlovoi, V.D.; Boiko, N.L.; Shemetun, A.M.; Kharchenko, T.I., 1981, Cytogenetic action of cyclohexanone. Gig. Sanit. 46(5):76-77. Abstract.

Eichbaum, F.W.; Yasaka, W.J., 1976, Antiarrhythmic effect of solvents: Propylene glycol, benzyl alcohol. Basic Res. Cardiol. 71:355-370.

Epstein, W.L., 1973, Report to RIFM, 26 November. (As cited by Opdyke, 1978b).

Fasano, R.; Randel, M.; Sadowski, L.; Wong, C. Analytical methods development for dimethyl methyl phosphonate, diiso-propyl methyl phosphonate and trimethylphosphate. Arthur D. Little, Inc. Report to the U.S. Army Toxic and Hazardous Material Agency, Aberdeen Proving Ground, MD 21010; September 1982.

Federal Register. Alcohol drug products for topical antimicrobial over-the-counter human use; establishment of a monograph and reopening of administrative record. United States Food and Drug Administration. 47:22324-22333; 1982.

Feldmann, R.J.; Maibach, H.I. 1970, Absorption of some organic compounds through the skin in man. J. Invest. Dermatol. 54:399-404.

Ficsor, G.; Lo Piccolo, G.M.N., 1972, Survey of pesticides for mutagenicity by the bacterial-plate assay method. EMS Newsl. 6:6-8.

Flavoring Extract Manufacturer's Association (FEMA), 1965, Survey of flavoring ingredient usage levels. Nos. 2745, 2376, 2058, 2371, 2866. Fd. Technol. Champaign 19(2) part 2:155. (As cited by Opdyke, 1973, 1975, 1978b,d,e).

Florin, I.; Rutberg, L.; Curvall, M.; Enzell, C.R., 1980, Screening of tobacco smoke constituents for mutagenicity using the Ames' test. Toxicology 15:219-232.

Food and Drug Administration, 1982, Benzyl alcohol may be toxic to newborns. FDA Drug Bulletin 12:10-11.

Food Chemicals Codex, 3rd edition, 1981, Specifications for flavor aromatic chemicals and isolates. Washington, DC:National Academy Press.

Food Chemical News Guide. Rothschild, L., Jr., ed., 1982, Washington, DC:Food Chemical News, Inc..

Furia, T.E.; Bellanca, N., 1975, Fenaroli's Handbook of Flavor Ingredients. Cleveland, Ohio:CRC Press.

Gage, J.C., 1970, The subacute inhalation toxicity of 109 industrial chemicals. Br. J. Ind. Med. 27:1-18. (As cited in NIOSH, 1978b).

Gardner, H.A., 1925, Physiological effects of vapors from a few solvents used in paints, varnishes and lacquers. Paint Manufrs. Assoc. of U.S. Circ. No. 250:89-149.

Gershanik, J.J.; Boecler, B.; George, W.; Sola, A.; Leitner, M.; Kapadia, C., 1981, The gasping syndrome: Benzyl alcohol (BA) poisoning? Clin. Res. 29:895A.

Gershenfeld, L., 1952, Benzyl alcohol in parenteral solutions. Am. J. Pharm. 124:399-403.

Gizhlaryan, M.S., 1966, [Toxicology of higher mercaptans.] Biol. Zh. Arm. 19:41-46. (As cited in NIOSH, 1978b).

Gleiberman, S.E.; Voronkina, T.M., 1972, Absorption of the repellent diethyltoluamide. Med. Parazitol. Parazit. Bolezni 41:189-197. Abstract.

Gleiberman, S.E.; Volkova, A.P.; Nikolaev, G.M.; Zhukova, E.V., 1975, A study on embryotoxic properties of the repellent diethyltoluamide. Farmakol. Toksikol. 2:202-205. Abstract.

Gleiberman, S.E.; Volkova, A.P.; Nikolaev, G.M.; Zhukova, E.V., 1976, Study on the long-term results of the use of repellents: I. Experimental study of the effect of long-term use of diethyltoluamide (DETA) repellent. Med. Parazitol. Parazit. Bolezn. 45:65-69.

Gosselin, R.E.; Hodge, H.C.; Smith, R.P.; Gleason, M.N., 1976, Clinical Toxicology of Commercial Products. Acute Poisoning. 4th Edition. Baltimore:The Williams and Wilkins Co..

Gozsy, B.; Kátó, L., 1957, Action of reticulo-endothelial-system stimulators on the histamine depleted rats. Arch. intern. pharmacodynamie 112:235-246.

Gozsy, B.; Kátó, L., 1958, Reticulo-endothelial system stimulating compounds and their mechanism of action. Can. J. Biochem. Physiol. 36:319-326.

Grimalt, F.; Romaguera, C., 1975, New resin allergens in shoe contact dermatitis. Contact Dermatitis 1:169-174.

Gruber, C.M., 1923a, The pharmacology of benzyl alcohol and its esters. I. The effect of benzyl alcohol, benzyl acetate and benzyl benzoate when given by mouth upon the blood pressure, pulse and alimentary canal. J. Lab. Clin. Med. 9:15-33.

Gruber, C.M., 1923b, The pharmacology of benzyl alcohol and its esters. II. Some of the effects of benzyl alcohol, benzyl benzoate and benzyl acetate when injected intravenously upon the respiratory and circulatory systems. J. Lab. Clin. Med. 9:92-112.

Gruber, C.M., 1924, Effect of benzyl alcohol and its esters, benzyl benzoate and benzyl acetate, upon kidney functions. J. Pharmacol. 23, Proc. 149. Abstract.

Gruber, C.M., 1925, The pharmacology of benzyl alcohol and its esters. IV. The diuretic effect of benzyl alcohol, benzyl acetate and benzyl benzoate. J. Lab. Clin. Med. 10:284-293.

Gryboski, J.; Weinstein, D.; Ordway, N.K., 1961, Toxic encephalopathy apparently related to the use of an insect repellent. N. Eng. J. Med. 264:289-291.

Gupta, P.K.; Lawrence, W.H.; Turner, J.E.; Autian, J., 1979, Toxicological aspects of cyclohexanone. Toxicol. Appl. Pharmacol. 49:(3):525-534.

Hagan, E.C.; Hansen, W.H.; Fitzhugh, O.G.; Jenner, P.M.; Jones, W.I.; Taylor, J.M.; Long, E.L.; Nelson, A.A.; Brouwer, J.B., 1967, Food flavorings and compounds of related structure. II. Subacute and chronic toxicity. Food Cosmet. Toxicol. 5(2):141-157.

Haight, E.A.; Harvey, Jr., J.G.; Singer, A.W.; Pope, C.R., 1980, Subchronic oral toxicity study of the insect repellent N,N,-diethyl-m-toluamide (m-DET). Iss. USAEHA 75-51-0034-80, AD-A082131; 23pp.

Harrison, J.W.E.; Abbott, D.D.; Packman, E.W., 1963, Fedn. Proc. Fedn. Am. Socs. Exp. Biol. 22:554. (As cited by Opdyke, 1978b).

Heick, H.M.C.; Shipman, R.T.; Norman, M.G.; James, W., 1980, Reye-like syndrome associated with use of insect repellent in a presumed heterozygote for ornithine carbamoyl transferase deficiency. J. Pediatr. 97:471-473.

Hellerstrom, S.; Lunden, B., 1951, Does the sensitizing power of various turpentine fractions regularly depend on oxidation products? Acta derm.-vener. 31:46-51. (As cited by Pirila et al., 1964).

Hellerstrom, S.; Thyresson, N.; Blohm, S. -G.; Widmark, G., 1953, Skin sensitivity to different terpenes and terpene fractions. Acta Derm. Venereol. 33:51-64.

Hellerstrom, S.; Thyresson, N.; Blohm, S. -G.; Widmark, G., 1957, Chemical aspects on turpentine eczema. Dermatologica 115:277-286.

Henry, S.A., 1933, Celery itch: Dermatitis due to celery in vegetable canning. Br. J. Dermatol. Syph. 45:301-309.

Henry, S.A., 1938, Further observations on dermatitis due to celery in vegetable canning. Br. J. Dermatol. Syph. 50:342-351.

Hoffman, E.; Milling, A., Jr.; Parmelee, D., 1969, Anal. Biochem. 32:386.

Hollingshaus, J.G.; Armstrong, D.; Toia, R.F.; McCloud, L.; Fukuto, T.R., 1981, Delayed toxicity and delayed neurotoxicity of phosphorothioate and phosphonothioate esters. J. Toxicol. Environ. Health 8:619-627.

Holmberg, B.; Malmfors, T., 1974, Cytotoxicity of some organic solvents. Environ. Res. 7(2):183-192.

Hoy, K.L., 1970, New values of the solubility parameters from vapor pressure data. J. Paint Technology 42:76-118.

Jenkins, R.L.; Gute, J.P.; Krasner, S.W.; Baird, R.B., 1980, The analysis and fate of odorous sulfur compounds in wastewaters. Water Res. 14:441-448.

Jenner, P.M.; Hagan, E.C.; Taylor, J.M.; Cook, E.L.; Fitzhugh, O.G., 1964, Food flavourings and compounds of related structure I. Acute oral toxicity. Food Cosmet. Toxicol. 2:327-343.

Jeppsson, R., 1975, Parabolic relationship between lipophilicity and biological activity of aliphatic hydrocarbons, ethers, and ketones after intravenous injections of emulsion formulations into mice. Acta Pharmacol. et Toxicol. 37:56-64.

Joint FAO/WHO Expert Committee on Food Additives, 1967, Toxicological Evaluation of Some Flavouring Substances and Non-nutritive Sweetening Agents. F.A.O. Nutr. Mtg. Rep. Ser. no. 44A, Geneva, WHO/Food Add./68.33:p63. (As cited by Opdyke, 1978b).

Jurgens, R.W., Jr., 1976, Preservatives for ophthalmic products. Drug Cosmet. Ind. 118:56, 58, 60.

Kane, H.F.; Roth, G.B., 1936, The relief of labor pains by the use of paraldehyde and benzyl alcohol. J.A.M.A. 107:1710-1714.

Kellner, T.P.; Hanes, M.A.; Fruin, J.T., 1981, Primary eye irritation potential of the insect repellents CHF1 and m-DEET. NTIS AD/A107 736/a:29pp.

Keplinger, M.L.; Frawley, J.P.; Tusing, T.W.; Woodard, G.; Dardin, V.J., 1961, Subacute oral and dermal toxicity of DEET (N,N-diethyl-m-toluamide). Fed. Proc. 20:432. Abstract.

Kida, H., 1978, Effects of temperature on percutaneous absorption of methyl salicylate. Fukuoka Igaku Zasshi. 69(5):208-222. Abstract.

King, B.M.; Solms, J., 1979, Interactions of flavor compounds in model food systems using benzyl alcohol as an example. J. Agric. Food Chem. 27:1331-1334.

Kirk-Othmer Encyclopedia of Chemical Technology, 3rd ed. Grayson, M.; Eckroth, D., eds., 1978, New York:John Wiley and Sons.

Kitagawa, H.; Saito, H.; Sakai, T.; Esumi, Y.; Miyoshi, K.; Sekine, S.; Ishii, N.; Mori, M.; Tazoe, R.,1979b, Absorption, distribution and excretion of methyl salicylate by dermal application to rabbits. Oyo Yakuri 18:967-971. Abstract.

Kligman, A.M., 1971, Report to RIFM, 20 April. (As cited by Opdyke, 1975).

Kligman, A.M., 1972, Report to RIFM, 3 November. (As cited by Opdyke, 1973).

Kligman, A.M., 1974, Report to RIFM, 4 June. (As cited by Opdyke, 1978e).

Kligman, A.M., 1975, Report to RIFM, 16 May. (As cited by Opdyke, 1978c).

Kligman, A.M., 1977, Report to RIFM, 23 May. (As cited by Opdyke, 1980).

Koeferl, M.T.; Miller, T.R.; Fisher, J.D.; Martis, L.; Garvin, P.J.; Darner, J.L., 1981, Influence of concentration and rate of intravenous administration on the toxicity of cyclohexanone in beagle dogs. Toxicol. Appl. Pharmacol. 59(2):215-229.

Kuhlmann, R.S.; Cameron, R.H.; Kolesari, G.L.; Wu, A., 1981, N,N diethyl-meta-toluamide: Embryonic sensitivity. Teratology 23:48A. Abstract.

Laboratoire Pharmacoetechnique Dubois and Vincent., 1964, Médicament gastro-protecteur administrable per os a base d'alcool benzylique. Fr. Patent No. 2.559M (Cl.A 61k-c07c), 7pp., June 1.

Lachman, L.; Urbanyi, T.; Weinstein, S., 1963, Stability of antibacterial preservatives in parenteral solutions. IV. Contribution of rubber closure composition on preservative loss. J. Pharm. Sci. 52:244-249.

Lacroix, R.; Ferragne, J., 1964, Methyl salicylate intoxication. I. Toxic effects in conscious and in anesthetized dogs. Bull. Trav. Soc. Pharm. Lyon 8(3):129. (As cited by Opdyke, 1978b).

Lamberg, S.I.; Mulrennan, J.A., 1969, Bullous reaction to diethyltoluamide (DEET). Arch. Dermatol. 100:582-586.

Lebowitz, H.; Young, R.; Galloway, S.; Brusick, D., 1981, The effect of N,N-diethyltoluamide (DEET) on sperm number, viability and head morphology in male rats treated dermally. Environ. Mutagenesis 3:370. Abstract.

Levenstein, I., 1975, Report to RIFM; 19 May. (As cited by Opdyke, 1978c).

Levenstein, I., 1975, Report to RIFM, 20 May. (As cited by Opdyke, 1978d).

Litton Bionetics, Inc., 1979a. Subchronic study (13-week) in mice. Dimethyl methylphosphonate (C-54762). Revised addendum report. Project No. 10608-12. Submitted by Litton Bionetics, Inc., Kensington, Maryland 20795 to Tracor Jitco, Inc., Rockville, Maryland 20852.

Litton Bionetics, Inc., 1979b. Subchronic study (13-week) in rats. Dimethyl methylphosphonate (C-54762). Revised addendum report. Project No. 10608-13. Submitted by Litton Bionetics, Inc., Kensington, Maryland 20795 to Tracor Jitco, Inc., Rockville, Maryland 20852.

Litton Bionetics, Inc., 1981. Subchronic study (13-week) in rats. Dimethyl methylphosphonate (C-54762). Final report. Project No. 10608-13. Submitted by Litton Bionetics, Inc., Kensington, Maryland 20795 to Tracor Jitco, Inc., Rockville, Maryland 20852.

Lur'e, A.A.; Gleiberman, S.E.; Tsizin, Y.S., 1978, Pharmacokinetics of the repellent N,N-diethyl-3-methylbenzamide. Med. Parazitol. Parazit. Bolezni 47:72-77. Abstract.

Lyman, W.J.; Reehl, W.F.; Rosenblatt, D.H. eds., 1982, Handbook of Chemical Property Estimation Methods. New York:McGraw-Hill Book Co..

Macht, D.I., 1918a, A pharmacologic and therapeutic study of benzyl alcohol as a local anesthetic. J. Pharmacol. Exp. Ther. 11:263-279.

Macht, D.I., 1918b, On the relation between the chemical structure of the opium alkaloids and their physiological action on smooth muscle with a pharmacological and therapeutic study of some benzyl esters. II. A pharmacological and therapeutic study of some benzyl esters. J. Pharmacol. Exp. Ther. 11:419-446.

Macht, D.I.; Hill, J.H., 1923, Concerning the antiseptic action of some benzyl compounds. Bull. Johns Hopkins Hosp. 34:154-157.

Macht, D.I.; Nelson, D.E., 1918, On the antiseptic action of benzyl alcohol. Proc. Soc. Exp. Biol. Med. 16:25-26.

Macko, J.A. Jr.; Weeks, M.H., 1980, Acute toxicity evaluation of N,N-diethyl-meta-toluamide (M-DET). U.S. Army Environmental Hygiene Agency, Report No. 75-51-0034-81-phase 6, order no. AD-A092 653/5:32pp.

Macmillan, K.L., 1973, The effect of benzyl alcohol on the oestrous cycle of cattle. Aust. Vet. J. 49:267-268.

Maibach, H.I.; Johnson, H.L., 1975, Contact urticaria syndrome - contact urticaria to diethyltoluamide (immediate-type hypersensitivity). Arch. Dermatol. 111:726-730.

Majors, P.A., 1971, Report to RIFM, 13 April. (As cited by Opdyke, 1975).

Manufacturing Chemists' Association (MCA)., 1972, Guide for Safety in the Chemical Laboratory, 2nd ed., New York:Van Nostrand Reinhold Co..

Marsden, C.; Mann, S., eds., 1963, Solvents Guide. New York:John Wiley and Sons, Inc.

Maruta, H.; Minami, K.; Yamagata, T.; Noda, K., 1977, Percutaneous absorption of methyl salicylate from medicated plaster in mice and humans. Kurume Med. J. 24(3):131-137.

Maruzzella, J.C.; Bramnick, E., 1961, The antibacterial properties of perfumery chemicals. Soap, Perfumery and Cosmetics 34:743-746.

Massoud, A.; Aly, A.; Shafik, H., 1980, Mutagenicity and carcinogenicity of cyclohexanone. Mutat. Res. 74(3):174. Abstract.

Maurer, T.H.; Weirich, E.G.; Hess, R., 1980, The optimization test in the guinea pig in relation to other predictive sensitization methods. Toxicology 15:163-171.

McCreery, M.J.; Hunt, W.A., 1978, Physico-chemical correlates of alcohol intoxication. Neuropharmacology 17:451-461.

Mellan, I., 1970, Industrial Solvents Handbook. Park Ridge, NJ:Noyes Data Corp.

Miyashita, K.; Robinson, A.B., 1980, Identification of compounds in mouse urine vapor by gas chromatography and mass spectrometry. Mech. Aging Dev. 13:177-184.

Monie, I.W., 1970, Hydronephrosis and hydroureter induced by teratogens in rat fetuses. Teratology 3:206-207. Abstract.

Moreno, O.M., 1973, Report to RIFM, 12 November. (As cited by Opdyke, 1798b).

Moreno, O.M., 1977, Report to RIFM, 7 October. (As cited by Opdyke, 1980).

Morgan, J.K., 1968, Iatrogenic epidermal sensitivity. Br. J. Clin. Pract. 22:261-264.

Morton, H.E., 1976, Alcohols In Disinfection, Sterilization, and Preservation. Block, S.S., ed. Philadelphia, PA: Lea and Febiger; pp301-318 (As cited by Fed. Reg., 1982).

Moss, H.V., 1974, Allergic contact dermatitis due to halotex solution. Archives of Dermatology 109:572. (As cited by Schneider, 1980).

Motoyoshi, K.; Toyoshima, Y.; Sato, M.; Yoshimura, M., 1979, Comparative studies on the irritancy of oils and synthetic perfumes to the skin of rabbit, guinea pig, rat, miniature swine and man. Cosmet. Toiletries 94(8):41-43, 45-48.

Murugesh, N.; Kumar, V.R.; Vembar, S.; Damodaran, C., 1981a, Studies on erythrocyte membrane. V. Haemolytic effect of methylsalicylate and its possible mechanism. Toxicol. Lett. 9:225-229.

Murugesh, N.; Kumar, V.R.; Vembar, S.; Damodaran, C., 1981b, Studies on erythrocyte membrane. VI: Stabilization by drugs against the haemolytic effect of methyl salicylate. Toxicol. Lett. 9:421-425.

Nacino, F.M.; Barreto, C.B.; Cruz, L.J., 1975, The effect of citrus oil on tumor production by DMBA. Kalikasan, Philipp. J. Biol. 4:240-247.

NIOSH Manual of Analytical Methods., 1978a, n-Butyl Mercaptan -- Standards Completion Program Validated Method No. 5350. Cincinnati:U.S. Department of Health, Education and Welfare, Public Health Service Center for Disease Control; pp.S350-1 to S350-9.

NIOSH Criteria for a Recommended Standard., 1978b, Occupational Exposure to n-Alkane Mono Thiols, Cyclohexanethiol, and Benzenethiol. U.S. Department of Health Education, and Welfare. DHEW(NIOSH) Publication No. 78-213; Sept.

Nishimura, H.; Kimura, N.; Shimaoka, N., 1950, Bacteriostatic and bactericidal effects of benzyl alcohol and related compounds. Japan. J. Pharm. Chem. 22:500-504. Abstract.

Ohmiya, Y.; Nakai, K., 1978, Interaction of benzyl alcohol with human erythrocytes. Jpn. J. Pharmacol. 28:367-373.

Ojiambo, H.P., 1971a, Catecholamine metabolism in methysalicylate myopathies. East Afr. Med. J. 48(5):236-238.

Ojiambo, H.P., 1971b, Certain aspects of metabolism in myopathies induced by methyl salicylate intoxication in the dog. East Afr. Med. J. 48(6):243-246.

Ojiambo, H.P., 1971c, Absorption, transport, and biotransformation of methysalicylate in the dog. East Afr. Med. J. 48(7):318-321.

Ojiambo, H.P., 1971d, Hindlimb metabolism in dogs intoxicated with methyl salicylate. East Afr. Med. J. 48(9):476-481.

Ojiambo, H.P., 1974, Circulatory changes in dogs intoxicated with methylsalicylate. In: Myocardiol. Afr. Proc. Int. Symp. Prev. Cardiol. Card. Metab. 1:97. (As cited in Opdyke, 1978b).

Oka, S., 1962 Studies on transfer of antiseptics to microbes and their toxic effect. VI. Toxic effect and adsorption of phenols and esters of acid antiseptics on bacterial cell. Agric. Biol. Chem. 26:515. (As cited by Opdyke, 1978c).

Opdyke, D.L.J., 1973, Fragrance raw materials monographs. Amyl benzoate. Food Cosmet. Toxicol. 11:495, 1081.

Opdyke, D.L.J., 1975, Monographs on fragrance raw materials. Phenylethyl phenylacetate. Food Cosmet. Toxicol. 13(Suppl.):907-908.

Opdyke, D.L.J., 1976, Inhibition of sensitization reactions induced by certain aldehydes. Food Cosmet. Toxicol. 14:197-198.

Opdyke, D.L.J., 1978a, Monographs on fragrance raw materials . ℓ-Limonene. Food. Cosmet. Toxicol. 16(Suppl.):809.

Opdyke, D.L.J., 1978b, Monographs on fragrance raw materials. Methyl salicylate. Food. Cosmet. Toxicol. 16(Suppl.):821-825.

Opdyke, D.L.J., 1978c, Monographs on fragrance raw materials. N-butyl salicylate. Food Cosmet. Toxicol. 16(Suppl.):663.

Opdyke, D.L.J., 1978d, Monographs on fragrance raw materials. Diethyl sebacate. Food. Cosmet. Toxicol. 16(Suppl.):705-706.

Opdyke, D.L.J., 1980, Fragrance raw materials monographs. Anisyl phenylacetate. Food Cosmet. Toxicol. 18:651.

Overman, D.O.; White, J.A., 1978, Comparative dose-response analysis of the teratogenic effects of methyl salicylate applied orally or topically to hamsters. Anat. Rec. 190:499. Abstract.

Overman, D.O., 1979, Percutaneous administration of teratogens: Effects of treatment with methyl salicylate and dimethyl sulfoxide in the hamster. Teratology 19:42A. Abstract.

Palmer, J.S., 1969, Toxicological effects of aerosols of N,N-diethyl-m-toluamide (Deet) applied on skin of horses. Am. J. Vet. Res. 30:1929-1932.

Park, B.K.; Leck, J.B., 1981, On the mechanism of salicylate-induced hypothrombinaemia. J. Pharm. Pharmacol. 33:25-28.

Pentz, R.; Schuett, A.,1978, A rapid gas-chromatographic method for the determination of drugs in clinical toxicology. Arch. Toxicol. 39(2):225-233.

Phillips, L. II; Steinberg, M.; Maibach, H.I.; Akers, W.A., 1972, A comparison of rabbit and human skin response to certain irritants. Toxicol. Appl. Pharmacol. 21:369-382.

Pienta, R.J., 1980, Transformation of Syrian hamster embryo cells by diverse chemicals and correlation with their reported carcinogenic and mutagenic activities. Chemical Mutagens: Principles and Methods for Their Detection 6:175-202.

Pinching, A.J.; Doving, K.B., 1974, Selective degeneration in the rat olfactory bulb following exposure to different odours. Brain Res. 82:195-204.

Pirila, V.; Siltanen, E., 1958, On the chemical nature of the eczematogenic agent in oil of turpentine. III. Dermatologica 117:1-8.

Pirila, V.; Siltanen, E.; Pirila, L., 1964, On the chemical nature of the eczematogenic agent in oil of turpentine. IV. The primary irritant effect of terpenes. Dermatologica 128:16-21.

Prokof'eva, V.G.; Migda, N.A., 1978, Gas chromatographic determination of DETA in blood and urine. Prom-st. Tovarov Bytovoi Khim. (Ref. Nauchno-Tekh. Sb.) 4:29. Abstract.

Rainsford, K.D.; Whitehouse, M.W., 1980, Anti-inflammatory anti-pyretic salicylic acid esters with low gastric ulcerogenic activity. Agents and Actions 10:451-456.

Regan, J.W.; Bjeldanes, L.F., 1976, Metabolism of (+)-limonene in rats. J. Agric. Food Chem. 24:377-380.

Regan, J.W.; Morris, M.M.; Nao, B.; Bjeldanes, L.F., 1980, Metabolism of limonene-1,2-epoxide in the rat. Xenobiotica 10:859-861.

Registry of Toxic Effects of Chemical Substances (RTECS), 1979 ed., Vol. 1 and 2. Lewis, R.J., Sr.; Tatken, R.L., eds., 1980, Cincinnati, Ohio:U.S. Dept of Health and Human Services (NIOSH).

Reich, W.J.; Button, H.; Nechtow, M.J., 1943, A new treatment for intractable pruritus vulvae. Am. J. Obstet. Gynecol. 45:1036-1038.

Reifenrath, W.G.; Hill, J.A.; Robinson, P.B.; McVey, D.L.; Akers, W.A.; Anjo, D.M.; Maibach, H.I., 1980, Percutaneous absorption of carbon ^{14}labeled insect repellents in hairless dogs. J. Environ. Pathol. Toxicol. 4:249-256.

Reifenrath, W.G.; Robinson, P.B.; Bolton, V.D.; Aliff, R.E. 1981, Percutaneous penetration of mosquito repellents in the hairless dog: Effect of dose on percentage penetration. Fd. Cosmet. Toxicol. 19:195-199.

Rengstorff, R.H.; John, P.P.; Sim, V.M., 1972, Cataracts induced in guinea pigs by acetone, cyclohexanone and dimethyl sulfoxide. Amer. J. Ophthalm. 72:308-3A. (As cited by Gupta et al., 1979).

Roe, F.J.C.; Peirce, W.E.H., 1960, Tumor promotion by citrus oils: Tumors of the skin and urethral orifice in mice. J. Nat. Cancer Inst. 24:1389-1403.

Rokstad, I., 1947, Skin reactions caused by fractions of oil of turpentine and hexanitrodiphenylamine. Br. J. Dermatol. 59:115-116. (Abstract).

Roth, G.B.; Kare, H.F., 1936b. Proceedings of the American Society of Pharmacology and Experimental Therapeutics, Annual Meeting, Washington, DC. (As cited by Roth and Kane, 1936a).

Sadée, W.; Beelen, G.C.M., 1980, Drug Level Monitoring: Analytical Techniques, Metabolism and Pharmacokinetics. New York:John Wiley and Sons. p417-423.

Sanchez de Rivera Vazquez, A.; Rodriguez Perez, A.; Izquierdo, Sanjose, M., 1977, Study of a penetrating agent in percutaneous absorption. I. Comparative study using dimethyl sulfoxide. Cienc. Ind. Farm. 9(5):133-136. (As cited in CA/087/157098 G).

Sauers, L.J.; Pulliam, F.R.; Fruin, J.T., 1981, The mutagenic potential of: triethylene glycol monohexyl ether; 3-(N-n-butyl-N-acetyl)aminopropionic acid ethyl ester; proprietary compound RH-398; N,N-diethyl-m-toluamide; N(n-hexyl) glutarimide. AD-A107 685/0; 54pp.

Sax, N.I., 1979, Dangerous Properties of Industrial Materials, 5th ed. New York:Van Nostrand Reinhold Co..

Schaaf, F., 1961, Chemische Konstitution und Wirkung im Akanthosetest. Dermatologica 123:362. (As cited by Opdyke, 1978e).

Schaefer, R.; Schaefer, W., 1982, Percutaneous absorption of various terpenes-menthol, camphor, limonen, isobornyl acetate, α-pinene - from bath preparations. Arzneim.-Forsch. 32:56-58. Abstract.

Schaffer, J.M.; Tilley, F.W., 1927, Further investigations of the relation between chemical constitution and the germicidal activity of alcohols and phenols. J. Bacteriology 14:259-273. (As cited by Fed. Reg., 1982).

Schmidt, C.H.; Acree, F. Jr.; Bowman, M.C., 1959 Fate of C^{14}-diethyltoluamide applied to guinea pigs. J. Econ. Entomol. 52:928-930.

Schneider, K.W., 1980, Contact dermatitis due to diethyl sebacate. Contact Dermatitis 6:506-507.

Schultheiss, E., 1959, Summi und Ekzem. Editio Cantor. Aulendorf i Wurtfenberg. (As cited by Opdyke, 1978e).

Seeman, P., 1972, The membrane actions of anaesthetics and tranquilizers. Pharmac. Rev. 24:583-655. (As cited by Beatty and Martin, 1978).

Sherman, R.A., 1979, Behavioral effects of acute aerosol exposure to N,N-diethyl-meta-toluamide (m-DET), USAEHA-75-51-0034-80, order no. AD-A076939:28 pp.

Silyanovska, K.; Stoichev, S.; Zolotovich, G.; Nachev, K., 1968, Cytotoxic effect of esters isolated from essential oils. C.R. Acad. Bulg. Sci.; 20(12):1337-1339. Abstract.

Smith, J.F.; Peterson, A.J.; Fairclough, R.J., 1979, Plasma hormone levels in the cow. II. Changes in progesterone and oestrogen after the intra-uterine administration of prostaglandin F2 α or benzyl alcohol. N.Z.J. Agric. Res. 22:227-231.

Snapper, I.; Grunbaum, A.; Sturkop, S., 1924, The decomposition and oxidation of benzyl alcohol and benzyl esters in the human organism. Nederland. Tijdschr. Geneeskunde 68:3125-3133. Abstract.

Snodgrass, H.L., Jr.; Nelson, D.C.; Weeks, M.H., 1980, Dermal penetration of the radiolabeled repellent N,N-Diethyl-m-toluamide (m-DET), phase 8. ISS USAEHA-75-51-0034-81, order no. AD-A092937:26pp.

Spencer, T.S.; Hill, J.A.; Feldman, R.J.; Maibach, H.I., 1979, Evaporation of diethyltoluamide from human skin in vivo and in vitro. J. Invest. Dermatol. 72:317-319.

Stecher, P.G. ed., 1968, The Merck Index. An Encyclopedia of Chemicals and Drugs. 8th ed., Rahway, NJ:Merck and Co., Inc..

Stekol, J.A., 1939, Studies on the mercapturic acid synthesis in animals. XI. The detoxification of benzyl chloride, benzyl alcohol, benzaldehyde and S-benzylhomocysteine in the rabbit and rat. J. Biol. Chem. 128:199-205.

Stoner, G.D.; Shimkin, M.B.; Kniazeff, A.J.; Weisburger, J.H.; Weisburger, E.K.; Gori, G.B., 1973, Test for carcinogenicity of food additives and chemotherapeutic agents by the pulmonary tumor response in strain A mice. Cancer Res. 33:3069-3085.

Strom, J.G.; Jun, H. W., 1974, Gastric irritation and bleeding after drug administration. J. Pharm. Sci. 63:1812. (As cited by Opdyke, 1978b).

Sutherland, A.M., 1937, The treatment of "broad ligament neuritis" by "A.B.A." J. Obstet. Gynaecol. Br. Emp. 44:343-348.

Swentzel, K.C., 1977, Investigation of N,N-diethyl-m-toluamide (m-Det) for dominant lethal effects in the mouse. USAEHA-51-0034-78 Order no. AD-A058414:12pp.

Szabo, K.T.; Free, S.M.; Birkhead, H.A.; Kang, Y.J.; Alston, E.; Henry M., 1971, The embryotoxic and teratogenic effects of various agents in the fetal mouse and rabbit. Toxicol. Appl. Pharmacol. 19:371-372. Abstract.

Tainter, M.L.; Throndson, A.H.; Moose, S.M., 1937, Studies in topical anesthesia. II. Further observations on the efficacy of the more common local anesthetics when used on the gums and oral mucosa. J. Am. Dent. Assoc. 24:1480-1487.

Takacs, E.; Warkany, J., 1968, Experimental production of congenital cardiovascular malformations in rats by salicylate posioning. Teratology 1:109-111.

Tamada, M.; Wada, Y.; Yamamoto, T.; Nagai, H.; Ushiyama, K.; Kobayashi, I., 1981, Antiinflammatory analgesic adhesive. Belg. Patent No. 888156. Nitto Electric Industrial Co., Ltd.; July 16. (As cited in CA/095/175823J).

Tenenbein, M., 1981, Toxic encephalopathy due to insect repellent ingestion. Vet. Hum. Toxicol. 23(5):363. Abstract.

Tilley, B.M., 1980, Rheumatoid arthritis: The disease and its treatment (Part 1). Am. Drug 182:35-39, 41.

Tolnai, S.; Morgan, J.F., 1962, Studies on the in vitro anti-tumor activity of fatty acids. VI. Derivatives of mono and di-carboxylic and unsaturated fatty acids. Can. J. Biochem. Physiol. 40:1367. (As cited by Opdyke, 1978d).

Townsend, G.F.; Brown, W.H.; Felauer, E.E.; Hazlett, B., 1962, Studies on the in vitro antitumor activity of fatty acids. IV. The esters of acids closely related to 10-hydroxy-2-decenoic acid from royal jelly against transplantable mouse leukemia. Can. J. Biochem. Physiol. 39:1765. (As cited by Opdyke, 1978d).

Traul, K.A.; Hink, R.J., Jr.; Kachevsky, V.; Wolff, J.S., III, 1981, Two-stage carcinogenesis in vitro: Transformation of 3-methylcholanthrene-initiated Rauscher murine leukemia virus-infected rat embryo cells by diverse tumor promoters. J. N.C.I. 66:171-176.

Van der Dool, H.; Kratz, P.D., 1963, J. Chromatogr. 11:463.

Voegtlin, C.; Livingston, A.E., 1919, Benzyl alcohol as a spinal anesthetic. J. Pharmacol. Proc. 13:513-514. Abstract.

Wade, A., 1977, Martindale. The Extra Pharmacopoeia. London:The Pharmaceutical Press.

Walash, M.I.; Hassam, S.M., 1978, A note on the identification of volatile oils in vaginal powders. J. Drug Res. 10(Iss 1-2):85-89.

Warkany, J.; Takacs, E., 1959, Experimental production of congenital malformations in rats by salicylate poisoning. Am. J. Pathol. 35:315-331.

Watabe, T.; Hiratsuka, A., 1980, Microsomal metabolism of d-limonene and mutagenicity of olefin oxides toward Salmonella typhimurium. J. Pharmacobio-Dyn. 3:S-7, S-22.

Watabe, T.; Hiratsuka, A.; Isobe, M.; Ozawa, N., 1980, Metabolism of d-limonene by hepatic microsomes to non-mutagenic epoxides toward Salmonella typhimurium. Biochem. Pharmacol. 29:1068-1071.

Watabe, T.; Hiratsuka, A.; Ozawa, N.; Isobe, M., 1981, A comparative study of the metabolism of d-limonene and 4-vinylcyclohex-1-ene by hepatic microsomes. Xenobiotica 11:333-344.

Webb, W.K.; Hansen, W.H., 1963, Chronic and subacute toxicology and pathology of methyl salicylate in dogs, rats and rabbits. Toxicol. Appl. Pharmacol. 5:576-587.

Wenrli, A.; Kovats, E., 1959, Helv. Chim. Acta. 42:2709.

Weifenbach, H., 1973, Intravenous toxicity of some glycols, glycerol, and neutral oils in the rat. Arzneim.-Forsch. 23(8):1087-1090. (As cited in CA/080/000463E).

Weir, R.J., 1971, Report to RIFM, 25 August. (As cited by Opdyke, 1973).

White, J.A., 1978, Intralitter teratogenic response variation: A relationship of fetal age to intrauterine position in hamsters? Teratology 17:37A. Abstract.

Whitehouse, M.W.; Rainsford, K.D., 1980, Esterification of acidic anti-inflammatory drugs suppresses their gastrotoxicity without adversely affecting their anti-inflammatory activity in rats. J. Pharm. Pharmacol. 32:795-796.

Williams, R.T., 1959, Detoxification Mechanisms. The Metabolism and Detoxification of Drugs, Toxic Substances and Other Organic Compounds. 2nd Ed. London:Chapman and Hall Ltd.; 324-349, 362.

Wohl, A.J., 1974, Report to RIFM 15 May. (As cited by Opdyke, 1973e).

Woo, D.C.; Hoar, R.M., 1971, The effect of methyl salicylate upon renal growth and methylene blue clearance in fetal rats. Teratology 4:244. Abstract.

Woo, D.C.; Hoar, R.M., 1972, "Apparent hydronephrosis" as a normal aspect of renal development in late gestation of rats: The effect of methyl salicylate. Teratology 6:191-196.

Wu, A.; Pearson, M.L.; Shekoski, D.L.; Soto, R.J.; Stewart, R.D., 1979, High resolution gas chromatography/mass spectrometric characterization of urinary metabolites of N,N-diethyl-m-toluamide (DEET) in man. J. High Resolut. Chromatogr. Chromatogr. Commun. 2(9):558-562.

Yamamoto, S.; Ito, Y.; Noda, S., 1967, Toxicity test of food additives by the disturbance of life cycles of Chlorella and Saccharomyces cerevisiae var. Sake. II. Bacteriostatic or bactericidal action of food preservatives and antimicrobials. Shokuhin Eiseigaku Zasshi 8:408. (As cited by Opdyke, 1978c).

Yankell, S.L., 1972, The effects of various vehicles on absorption rates in skin. Advan. Biol. Skin 12:511-522.

Yasaka, W.J.; Eichbaum, F.W.; Oga, S.,1979a, Antiarrhythmic effects of solvents: II. Effects of propylene glycol and benzyl alcohol on the effective refractory period of isolated rabbit atria. Cardiovasc. Res. 13:711-716.

Yasaka, W.J.; Eichbaum, F.W.; Oga, S., 1979b, Antiarrhythmic effects of solvents. III. Effects of propylene glycol and benzyl alcohol on contractile force of isolated rabbit heart. Cardiovasc. Res. 13:717-722.

Zadikoff, C.M., 1979, Toxic encephalopathy associated with use of insect repellent. J. Pediatr. 95:140-142.

Zaitsev, A.N.; Rakhmanina, N.L., 1974, Toxic properties of phenylethanol and cinnamic alcohol derivates. Vopr. Pitan. 33(5):48-53. (As cited in CA/082/069039E).

Zakamardin, I.A., 1969, Toxicity of diethyltoluamide for laboratory and agricultural animals. Uch. Zap. Kazan. Vet. Inst. 105:275-280. Abstract.

Zlatkis, A.; Liebich, H.M., 1971, Profile of volatile metabolites in human urine. Clin. Chem. 17:592-594.

Zlatkis, A.; Bertsch, W.; Bafus, D.A.; Liebich, H.M., 1974, Analysis of trace volatile metabolites in serum and plasma. J. Chromatogr. 91:379-383.

Zsolnai, T., 1960, Versuche zur entdeckung neuer fungistatika. I. Phenol-derivate. Biochem. Pharmac. 5:1. (As cited by Opdyke, 1978c).

Zulaica, J.; Guiochon, G., 1963, Bull. Soc. Chim. France, 1242.

Zweifler, A.J.; Sanbar, S.S., 1969, Inhibition of platelet adhesiveness and aggregation by benzyl alcohol and phenol. Thromb. Diath. Haemorrh. 21:362-366.

☆ U.S. GOVERNMENT PRINTING OFFICE: 1983—659-005/2025

AFAMRL-TR-82-87

AD-B070947

ERRATA

AFAMRL-TR-82-87, Entitled "Development of Candidate Chemical Simulant List: The Evaluation of Candidate Chemical Simulants Which May Be Used in Chemically Hazardous Operations, dated December 1982, is changed by replacing the attached Cover and DD Form 1473.

This document has been cleared for public release at this time.

Current DTIC Accession Number: ADB 070947L

Kenneth M. Zimmerman

KENNETH M. ZIMMERMAN
AFAMRL STINFO OFFICER

AFAMRL-TR-82-87

DEVELOPMENT OF CANDIDATE CHEMICAL SIMULANT LIST: THE EVALUATION OF CANDIDATE CHEMICAL SIMULANTS WHICH MAY BE USED IN CHEMICALLY HAZARDOUS OPERATIONS

ARTHUR D. LITTLE, INC.

ACORN PARK
CAMBRIDGE, MA 02140

DECEMBER 1982

Approved for public release; distribution unlimited

AIR FORCE AEROSPACE MEDICAL RESEARCH LABORATORY
AEROSPACE MEDICAL DIVISION
AIR FORCE SYSTEMS COMMAND
WRIGHT-PATTERSON AIR FORCE BASE, OHIO 45433

NOTICES

When US Government drawings, specifications, or other data are used for any purpose other than a definitely related Government procurement operation, the Government thereby incurs no responsibility nor any obligation whatsoever, and the fact that the Government may have formulated, furnished, or in any way supplied the said drawings, specifications, or other data, is not to be regarded by implication or otherwise, as in any manner licensing the holder or any other person or corporation, or conveying any rights or permission to manufacture, use, or sell any patented invention that may in any way be related thereto.

Please do not request copies of this report from Air Force Aerospace Medical Research Laboratory. Additional copies may be purchased from:

National Technical Information Service
5285 Port Royal Road
Springfield, Virginia 22161

Federal Government agencies and their contractors registered with Defense Technical Information Center should direct requests for copies of this report to:

Defense Technical Information Center
Cameron Station
Alexandria, Virginia 22314

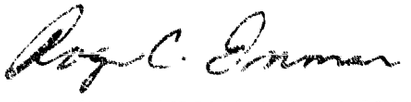
TECHNICAL REVIEW AND APPROVAL

AFAMRL-TR-82-87

This report has been reviewed by the Office of Public Affairs (PA) and is releasable to the National Technical Information Service (NTIS). At NTIS, it will be available to the general public, including foreign nations.

This technical report has been reviewed and is approved for publication.

FOR THE COMMANDER



ROGER C. INMAN, Colonel, USAF
Chief
Toxic Hazards Division
Air Force Aerospace Medical Research Laboratory

SECURITY CLASSIFICATION OF THIS PAGE (When Data Entered)

REPORT DOCUMENTATION PAGE

READ INSTRUCTIONS BEFORE COMPLETING FORM

1. REPORT NUMBER: AFAMRL-TR-82-87	2. GOVT ACCESSION NO.
3. RECIPIENT'S CATALOG NUMBER	
4. TITLE (and Subtitle): Development of Candidate Chemical Simulant List: The Evaluation of Candidate Chemical Simulants Which May Be Used in Chemically Hazardous Operations	5. TYPE OF REPORT & PERIOD COVERED: Final Report, Work Order #1 Jun 15, 1982 - Dec 15, 1982
	6. PERFORMING ORG. REPORT NUMBER: 87638-01
7. AUTHOR(s): Arthur D. Little, Inc. Acorn Park Cambridge, MA 02140	8. CONTRACT OR GRANT NUMBER(s): F33615-81-D-0508/0001
9. PERFORMING ORGANIZATION NAME AND ADDRESS: Arthur D. Little, Inc. Acorn Park Cambridge, MA 02140	10. PROGRAM ELEMENT, PROJECT, TASK AREA & WORK UNIT NUMBERS: 63745F 27220027 & 62202F 63020155
11. CONTROLLING OFFICE NAME AND ADDRESS: Air Force Aerospace Medical Research Laboratory, Aerospace Medical Division, Air Force Systems Command, Wright-Patterson AFB, Ohio 45433	12. REPORT DATE: December 1982
	13. NUMBER OF PAGES: 144
14. MONITORING AGENCY NAME & ADDRESS (if different from Controlling Office)	15. SECURITY CLASS. (of this report): UNCL
	15a. DECLASSIFICATION DOWNGRADING SCHEDULE

16. DISTRIBUTION STATEMENT (of this Report)

Approved for Public Release, Distribution Unlimited

17. DISTRIBUTION STATEMENT (of the abstract entered in Block 20, if different from Report)

18. SUPPLEMENTARY NOTES

Contact: Ms Marilyn E. George
AFAMRL/THB (255-5150)(area code 513)
WPAFB, OH 45433

19. KEY WORDS (Continue on reverse side if necessary and identify by block number)

Chemical defense
Chemical simulants list
Toxicology
Uptake chemical simulants

20. ABSTRACT (Continue on reverse side if necessary and identify by block number)

Nonhazardous chemical simulants of chemical warfare agents are needed by the United States Air Force (USAF) to test the effectiveness of protective equipment and decontamination procedures both in the laboratory and under full operational conditions. Selected candidate simulants, when dispersed, should mimic the physical characteristics of the actual agents as closely as possible, but induce no physiological effects in exposed personnel. Additionally, their uptake should be quantifiable in biological fluids, preferably urine or saliva.

DD FORM 1 JAN 73 1473 EDITION OF 1 NOV 65 IS OBSOLETE

SECURITY CLASSIFICATION OF THIS PAGE (When Data Entered)

In an initial task (Report No. AFAMRL-TR-82-28), seven candidates were proposed, four in the volatile category, the remaining three in the intermediate volatility range. All candidates in the low and non-volatile range were eliminated. This report is a continuation and supplementation of the initial task. The objectives of this task were threefold:

(1) to provide additional data for the proposed candidate simulants dipentene, methyl benzoate and benzyl alcohol by means of in-depth literature searches encompassing both computerized data bases and a manual search of the older literature;

(2) to fully evaluate twelve possible candidate simulants under more flexible simulant criteria; and,

(3) to develop a list of candidate simulants in the low and non-volatile categories.

Computerized literature searches were conducted for the twelve possible candidate simulants under more flexible intake simulant criteria as well as for dimethyl methylphosphonate, a compound selected for evaluation by the USAF. The twelve possible candidates included: cyclohexanone, n-dodecanethiol, methyl salicylate, dihexyl ether, dypnone, n-aminopropyl morpholine, n-(2-hydroxyethyl) morpholine, butyl salicylate, di(2-ethyl hexyl) ether, 2-undecanol, 2-hydroxyethyl-n-octyl sulfide and n,n-diethyl-m-toluamide.

Full assessments of the potential health hazards associated with exposure to n-dodecanethiol, methyl salicylate, butyl salicylate and n,n-diethyl-m-toluamide were completed. All of these compounds meet the majority of USAF criteria for candidate simulants. Cyclohexanone was disqualified for reasons of toxicity, while the available toxicological data for the seven remaining candidates were considered inadequate for full assessment of hazard.

A list of candidate chemical simulants in the low and non-volatile categories (vapor pressure 0.03 - 10^{-4} mm Hg) was developed. Six chemicals: diethyl sebacate, dibenzyl ether, isoamyl benzoate, anisyl phenylacetate, n-octyldecanethiol and phenylethyl phenylacetate are proposed as possible candidate simulants. All of these proposed candidate simulants meet majority of the physical chemical specifications, have low orders of and most have documented human exposure data and/or are approved for use foods and other consumer products.